REMARKS

I. Status of the Claims

Claims 27, 28, 37-42 and 51-92 are pending in the application. Claims 37-42, 51-81, 83, 84 and 92 have been withdrawn from consideration by the Examiner as being drawn to a non-elected invention. No claims have been amended or added. By this amendment, no new matter has been added to the application.

II. Priority

Pursuant to the Examiner's request, the specification on page 1, in the paragraph beginning on line 6, has been amended to reflect that Ser. No. 10/214,286 is now issued U.S. Patent No. 6,852,737.

III. Claim Rejections Under 35 U.S.C. § 102(b)

Claims 27, 28, 82 and 85-91 are rejected as allegedly anticipated by Sartani *et al.*, U.S. Patent No. 5,767,136 ("Sartani") and Testa *et al.* (1997) *Cardiovascular Drug Reviews* 15(3):187-219 ("Testa"). The Examiner alleges that since both Sartani and Testa disclose lercanidipine, each reference anticipates the pending claims to Form II lercanidipine. The rejection is respectfully traversed, on the grounds that neither Sartani nor Testa discloses Form II lercanidipine.

Anticipation requires that every element set forth in a claim be disclosed explicitly or inherently in a single reference. The instant claims are directed to a crystalline polymorph of lercanidipine that is designated "Form II," and which is identifiable by its physical characteristics, e.g., characteristic peaks obtained upon X-ray diffraction. Neither Sartani nor Testa discloses a crystalline lercanidipine having X-ray diffraction peaks that are characteristic of Form II or having the other physical properties of the Form II polymorph. Thus, neither Sartani nor Test explicitly discloses lercanidipine Form II lercanidipine. Neither does Testa or Sartani implicitly disclose lercanidipine Form II. Hence, neither Sartani nor Testa sets forth conditions for making lercanidipine that would be expected to yield Form II. Example 3 of Sartani cited by the Examiner includes only a general discussion of recrystallization of lercanidipine hydrochloride. Example 3, however, fails to provide any guidance as to which crystallization conditions would result in Form

II. Testa fails to provide any guidance useful for the crystallization of lercanidipine or for obtaining lercanidipine polymorphs. Thus, the section of Testa on page 189 pointed out by the Examiner merely describes the physico-chemical properties of lercanidipine without reference to *any* crystalline form or methods of making crystalline lercanidipine. The physico-chemical properties for lercanidipine disclosed in Testa do *not* describe Form II lercanidipine.

Crystallization conditions can and often do determine which polymorphic form of a compound is obtained. The Examiner points to no crystallization conditions --no particular starting material, solvent, temperature or cooling rate, no instructions to seed or not seed, no filtering or drying conditions -- in either Sartani or Testa that would invariably lead to Form II. These conditions are very important and can be determinative of the polymorphic form obtained, as illustrated from various other instances in the patent literature:

(1) Different polymorphs can be obtained from different solvents. See, e.g.,:

- U.S. Patent No. 5,872,132. Paroxetine hydrochloride anhydrate form B obtained from n-butanol (Ex. 7) v. form C obtained from toluene (Ex. 8).
- WO 01/15700. N-methyl-N-(3-{3-[2-thienylcarbonyl]-pyrazol-[1,5-α]-pyrimidin-7-yl}phenyl)acetamide Form I obtained from acetone (Ex. 2) or acetone/dichloromethane (Ex. 4) v. Form II obtained from methanol (Ex. 3).
- WO 00/78729. Lansoprazole form II with small amount of form I obtained from ethanol (Ex. 1) v. form I obtained from acetone (Ex. 2).

(2) Different polymorphs may also be obtained from the same solvent, depending on variations in crystallization conditions or drying steps. Even minor variations in conditions can result in a different crystalline product. See, e.g.,:

- U.S. Patent No. 5,248,699. Discloses that sertraline Forms I, II, and IV may be formed from the same organic solvents. Forms II and IV are formed by rapid crystallization. Slow crystallization or granulation of sertraline hydrochloride produces Form I. '699 Patent at col. 10, lines 45-49. Furthermore, the sertraline

polymorphs can be interconverted by heating or granulation. Id. at col. 10, lines 50-55.

U.S. Patent No. 5,412,095. Three polymorphs of terazosin monohydrochloride can be obtained from the same starting material (terazosin monohydrochloride methanolate) using the same solvent (ethanol). Terazosin Form I was obtained following dissolving terazosin monohydrochloride methanolate in hot absolute ethanol, cooling slowly to ambient temperature and standing overnight, and washing with dry acetone. (Ex. 5). Terazosin Form II was obtained by heating a slurry of terazosin monohydrochloride methanolate in absolute ethanol under reflux for approximately 24 h and cooling. (Ex. 6). Terazosin Form III was obtained by heating a slurry of terazosin monohydrochloride methanolate in absolute ethanol at 50°C for 30 min, followed by cooling in an ice bath and filtering. (Ex. 8).

- U.S. Patent No. 5,120,850. Describes obtaining different polymorphs of famotidine from the same solvents, depending on the cooling rate used during crystallization. Form A is obtained by starting with a hot solution and using a relatively slow cooling rate. '850 Patent at col. 2, lines 20-23. Form B is obtained by rapid cooling, which leads to rapid oversaturation. '850 Patent at col. 2, lines 23-29. Hence, Form A can be obtained by crystallization during slow cooling from boiling water or hot 50% methanol, 50% aqueous isopropanol, whereas Form B can be obtained from boiling water or hot 75% methanol, 50% aqueous isopropanol by placing the crystallization solution in an ice bath or pouring over ice (compare Ex. I/1, I/2 and I/4 to Ex. II/1, II/2, and II/3).

Thus, the foregoing examples illustrate that general guidance as to choice of solvents, cooling and drying conditions is not sufficient guidance to allow one of ordinary skill in the art to reproducibly obtain a particular polymorph. It cannot be presumed that all crystallization procedures falling within a general guidance for crystallization conditions will yield the same crystalline form.

With respect to the instant claims, the application makes clear that a simple reference to "crystalline lercanidipine" cannot be interpreted as a reference to Form II or indeed any other

particular crystalline form. The application discloses that it is possible to obtain at least four different crystalline forms of lercanidipine hydrochloride. Forms I and II are described in the application. Furthermore, the present specification discloses that lercanidipine hydrochloride crystalline Forms III and IV exist as well. *See* specification at page 13, lines 18-23. Hence, it is clear that crystalline lercanidipine hydrochloride can be present in several different physical forms. Each of these lercanidipine crystalline forms is obtainable by crystallization from, e.g., a "protic" solvent, depending on the precise conditions of crystallization and/or on the starting material.

With reference to the documents cited by the Examiner, Testa does not describe *any* crystallization conditions. Sartani does not describe crystallization conditions with such particularity that they would invariably lead to a particular lercanidipine crystalline form without the possibility of variation. Moreover, there will be sets of conditions that will have inherent variability. The Court of Appeals for the Federal Circuit has held that a prior art method for preparing crystalline forms does not anticipate a later-claimed crystalline form unless the method invariably leads to the claimed form. *Glaxo Inc. v Novopharm Ltd.*, 34 USPQ2d 1565, 52 F.3d 1043, 1047 (Fed. Cir. 1995), *cert. denied*, 516 US 988 (1995). There is no condition disclosed in Testa or Sartani that would lead invariably to Form II lercanidipine.

The present specification also dramatically illustrates that both lercanidipine hydrochloride Form I and lercanidipine hydrochloride Form II can be obtained following recrystallization from the same solvent, 2-propanol, depending on the conditions used. Example 4 of the present specification discloses preparation of Form I, by dissolving crude lercanidipine hydrochloride in 2-propanol under strong reflux and stirring, filtering, cooling to 40°C, maintaining the solution at 35°C for 24 h, then at 30°C for an additional 24 h, followed by filtering at 30°C, washing with 2-propanol, and drying at 70°C for 24 h. Example 10, by comparison, discloses preparation of Form II, by dissolving crude lercanidipine hydrochloride in a mixture of 2-propanol and water (8:2) at 60°C, filtering, cooling the solution to 25°C and stirring for 72 h at that temperature followed by collection of precipitate and drying. Thus, the instant specification itself illustrates the influence of crystallization conditions on the physical form that can be recovered. Both of the methods set forth in Examples 4 and 10 fall within the methods for "recrystallization of the crude [lercanidipine] hydrochloride compound from a solution of the compound in...a protic

solvent," including isopropanol, and optionally including water that are set forth in Sartani (*see* column 7, lines 44-46, 56, and 61). Yet each method produces a different crystalline form.

Applicants submit that the foregoing is but one demonstration that methods falling within the teachings of Sartani can be used to obtain different polymorphs. Thus, Sartani cannot in any meaningful way disclose the "same" methods of preparation of crystalline lercanidipine hydrochloride that will invariably produce one form of lercanidipine or another. Furthermore, as discussed above, Testa does not disclose *any* method of preparing crystalline forms of lercanidipine. Accordingly, the claimed crystalline lercanidipine hydrochloride Form II is not necessarily described in Sartani or Testa, nor is it explicitly disclosed.

For the reasons set forth above, Applicants submit that claims 27, 28, 82 and 85-91 are not anticipated by Sartani or Testa. Reconsideration of these claims and withdrawal of the rejection thereof under 35 U.S.C. § 102(b) is requested.

IV. Claim Rejections Under 35 U.S.C. § 103(a)

Claims 27, 28, 82 and 85-91 are rejected as allegedly obvious over the combined teachings of Sartani and Testa in view of Haleblian *et al.* (1969) *J. Pharmaceutical Sci.* 58(8):911-929 ("Haleblian"); Chemical & Engineering News, Feb. 2003; Brittain *et al.* (1999) *Polymorphism in Pharmaceutical Sci.* pages 1-2, 185 ("Brittain"); Taday *et al.* (2003) *J. Pharm. Sci.* 92(4):831-838 ("Taday"); U.S. Pharmacopia #23, National Formulary #18 (1995); Muzaffar *et al.* (1979) *J. Pharmacy (Lahore)* 1(1):59-66 ("Muzaffar"); Jain *et al.* (1986) *Indian Drugs* 23(6):315-329 ("Jain"); and *Concise Encyclopedia Chemistry* (1993) 872-873.

The Examiner contends that Sartani and Testa teach crystal forms of lercanidipine, as well as pharmaceutical compositions. The Examiner further contends that Haleblian, Muzaffar, Jain, Taday and Brittain teach that compounds exist as polymorphs, and that Chemical & Engineering News, Muzaffar, the U.S. Pharmacopia and the Concise Encyclopedia of Chemistry teach that at any particular temperature and pressure, only one polymorph is stable. According to the Examiner, the claimed crystalline Form II and its properties are suggested by the cited references, and therefore, it would have been obvious to one of skill in the art in view of the references that lercanidipine would exist in different polymorphic forms.

Applicants respectfully traverse this rejection. First, there is no suggestion in either Sartani or Testa, or in any of the secondary references to modify or combine their teachings to arrive at the claimed lercanidipine Form II polymorph. As discussed above, Sartani provides only a *general discussion* of the crystallization of lercanidipine and does not explicitly or inherently disclose lercanidipine Form II. Furthermore, Testa does not remedy the deficiencies of Sartani because Testa fails to disclose any crystallization of lercanidipine or any lercanidipine polymorph. Neither Sartani nor Testa provides any guidance as to the properties of Form II or methods of making the polymorph. The secondary references cited by the Examiner do not cure the deficiencies of Sartani and Testa. Furthermore, as illustrated above, crystallization conditions – temperature, starting material, solvents, cooling rate, etc. – can and often do influence the polymorph form that results, and therefore, one skilled in the art would not have a reasonable expectation of success by following the teachings of Sartani, Testa and the secondary references, of finding crystallization conditions that would produce lercanidipine Form II. Finally, since none of the references cited by the Examiner discloses lercanidipine Form II or a method of making it, the references, either alone or combined, do not teach or suggest each and every claim limitation.

For the reasons set forth above, Applicants submit that claims 27, 28, 82 and 85-91 are not obvious over Sartani and Testa in view of Haleblian, Chemical & Engineering News, Brittain, Taday, U.S. Pharmacopia, Muzaffar, Jain, and the Concise Encyclopedia Chemistry. Reconsideration of these claims and withdrawal of the rejection thereof under 35 U.S.C. § 103(a) is requested.

V. Rejections Under 35 U.S.C. § 112, First Paragraph

Claims 89-91 are rejected under 35 U.S.C. § 112, first paragraph for allegedly failing to comply with the written description and enablement requirements. With regard to written description, the Examiner contends that the specification fails to describe whether or how crystalline Form II would be maintained during preparation of the pharmaceutical composition, and fails to describe the pharmaceutical compositions in terms of X-ray diffraction or other physical data showing that the claimed polymorphic form is maintained. The Examiner also contends that the specification does not describe how Form II will be maintained when used in treatment. The Examiner cites Haleblian, Wall (1986) *Pharmaceutical Manufacturing* 3(2):33-34 and Jain as allegedly teaching that manufacturing processes affect polymorphs; Taday as allegedly teaching that

incorrect storage or tablet preparation can affect the polymorphic state of a drug; and Doelker (2002) *Annales Pharmaceutiques Francaises* 60(3):161-176 as allegedly teaching that the environment of a polymorph can affect the polymorphic state. Furthermore, the Examiner cites Chemical & Engineering News as allegedly teaching that the formulation of drugs in metastable forms will cause the drug to convert to its most stable form and Otsuka *et al.* (1999) *Chem. Pharm. Bull.* 47(6):852-856 as allegedly teaching that a particular drug, carbamazepine, changes polymorphic form during preparation and formulation.

With regard to the enablement rejection, the Examiner contends that undue experimentation would be required to make pharmaceutical compositions containing crystalline Form II of lercanidipine. The Examiner bases her rejection on the content of the disclosure and the breadth of the claims, the level of unpredictability in the art, and the allegedly poor amount of direction provided in the specification.

Applicants respectfully traverse the rejection of claims 89-91 as allegedly lacking written description. Applicants submit that the Examiner has not met her burden of showing that the written description is inadequate. The description is presumed to be adequate unless or until sufficient evidence or reasoning to the contrary is presented to rebut the presumption. *See In re Marzocchi*, 439 F.2d 220, 224 (C.C.P.A. 1971). None of the references cited by the Examiner teaches that *lercanidipine Form II* changes to another polymorphic form during manufacture, formulation or storage. The cited references either provide a general teaching that a polymorphic form (and especially a metastable polymorphic form) of a chemical *may* change during manufacture, formulation or storage, or disclose examples of chemical compounds *other than* lercanidipine where a polymorphic form has changed.

As disclosed in the specification, lercanidipine Form II is a *stable* polymorph that has a high melting point (197-201°C), a lower solubility in aqueous media and in absolute ethanol compared to lercanidipine Form I, exhibits no weight loss up to its melting point in gravimetric analysis, and is non-hygroscopic. *See* specification at page 11, line 19-22; page 40, lines 15-17; page 42, lines 1-2; and Example 15, pages 42-43. It is well known in the art that crystalline solids generally make better active pharmaceutical ingredients ("API"). *See Remington: The Science and Practice of Pharmacy 20th ed.* (Alfonso R. Gennaro, ed., 2000), page 705 (attached hereto at Exhibit A). Furthermore, it is well known that stable polymorphs are usually desired for APIs because

metastable forms are prone to chemical and physical instability. *See, e.g.,* Exhibit A at page 706; Singhal & Curatolo (2003) *Adv. Drug Delivery Rev.* 56:335-347 at 336-337 (attached hereto at Exhibit B). Lercanidipine Form II is a stable polymorph that is desirable for pharmaceutical formulation. Furthermore, the specification discloses a number of suitable pharmaceutical excipients for use in the lercanidipine Form II pharmaceutical compositions. Therefore, the specification conveys with reasonable clarity to one skilled in the art that the applicants were in possession of the claimed pharmaceutical compositions.

For the reasons set forth above, Applicants submit that claims 89-91 are adequately described in the specification. Reconsideration of these claims and withdrawal of the rejection thereof under 35 U.S.C. § 112, first paragraph is requested.

Applicants also respectfully traverse the rejection of claims 89-91 as allegedly lacking enablement. First, as pointed out above with respect to the written description rejection, lercanidipine Form II is a *stable* polymorph, and a limited number of suitable pharmaceutical excipients for use in compositions containing Form II are disclosed in the specification. Second, pharmaceutical compositions containing a polymorphic form of an active ingredient and methods of making such compositions are well known in the art. *See, e.g., Physicians' Desk Reference* 58th ed. (Thomson 2004) for representative examples of drug formulations containing crystalline APIs in different formulations – TIAZAC®, REMERONSolTab®, ZITHROMAX®, ZOLOFT® and AMBIEN® (attached hereto at Exhibit C). Moreover, a pharmaceutical composition (tablet) containing microcrystalline lercanidipine hydrochloride, lactose, microcrystalline cellulose, sodium starch glycollate, povidone and magnesium stearate is known and is available by prescription under the name ZANIDIP®. *See* ZANIDIP® prescribing information, available at http://www.pbs.gov.au/pi/smpzanid31205.pdf, last visited March 20, 2007 (attached hereto at Exhibit D). Thus, the Examiner has provided no reasonable basis to believe that the specification fails to enable the full scope of claims 89-91. The rejection should thus be withdrawn.

For the reasons set forth above, Applicants submit that claims 89-91 are enabled by the specification. Reconsideration of these claims and withdrawal of the rejection thereof under 35 U.S.C. § 112, first paragraph is requested.

VI. CONCLUSION

This application is believed to be in condition for allowance, which is earnestly solicited.

Dated: March 21, 2007

Respectfully submitted,

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EXHIBIT A

REMINGTON

The Science and Practice of Pharmacy

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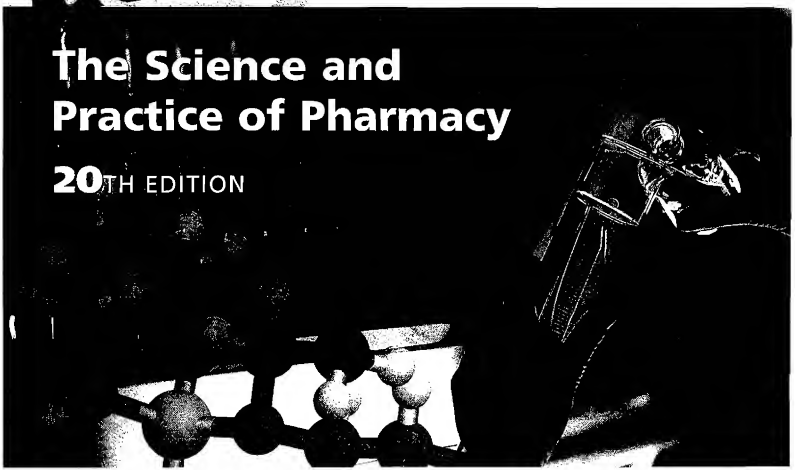

20 TH EDITION

Remington: The Science and Practice of Pharmacy

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pH-SOLUBILITY PROFILES

For a weak base, a plot of solubility versus pH will show the highest solubility at low pH and the lowest solubility at high pH; for weak acids, the opposite is true. Such plots give a graphic view of the impact of ionization on solubility for an NCE. The pH range of the small intestine, where oral absorption generally occurs, is approximately 6.5 to 8. It is undesirable to have a compound totally charged or uncharged in this region. If it is entirely charged, there are no un-ionized species that can be transported across the GI membrane. If it is totally uncharged, there are no charged species to enhance solubility. For a monoprotic NCE, the pK_a denotes the pH where the number of charged and uncharged species in solution are equal. On the ionized side of the pK_a, the solubility of the salt limits the maximum solubility. The solubility decline at very low pHs is due to activity and solubility-product effects.[3-5] On the un-ionized side, the solubility of A^0 (the intrinsic solubility) marks the lowest solubility. Salts promote a saturated solution to be formed at a pH that is on the ionized side of the pK_a. They cannot alter the pK_a or the intrinsic solubility. Using these parameters, a qualitative pH-solubility profile can be constructed. Figure 38-5 shows pH-solubility profiles for different counter-acid salts.

The synthesis of salts depends on

1. A proton-exchange reactivity between A^0 and the counter-acid/base
2. A long-range order that permits crystal formation.

The discussion that follows will focus on forming salts from weak bases, because they comprise the majority of the new drug candidates. Weak acids would be treated analogously.

SALT-FORMING REACTIVITY POTENTIAL

In order for a salt to form, both the weak base, A^0, and the counter-acid, HAn, must have sufficiently different pK_a values

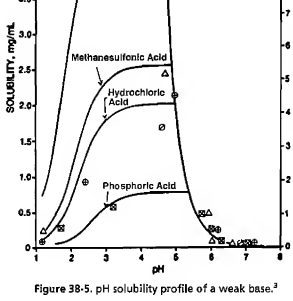

Figure 38-5. pH solubility profile of a weak base.[3]

such that a Brönsted-Lowry proton transfer from HAn to A^0 can take place. Table 38-2 gives potential counter-ions and their pK_a values from a listing of all drugs approved worldwide from 1963 to 1996. An acid–base proton transfer should be possible as long as the pK_a of HAn is less than that of the weak base A^0 (recall that the pK_a of A^0 is referenced to its protonated form A^0H^+; see *Solid-State Character*, page 702). If ΔpK_a is defined as

$$\Delta pK_a = pK_a \text{ (weak base)} - pK_a (HAn) \quad (12)$$

a salt-forming reaction should be possible as long as ΔpK_a is positive. For example, a succinate salt (pK_a 4.2) with doxylamine (pK_a 4.4) is possible[6] where the ΔpK_a is 0.2. Nevertheless, the greater the ΔpK_a, the greater the probability that a salt can be formed. Because the pK_a values in Table 38-2 are calculated for an aqueous environment, this rule must be used only as a guide for salt-forming reactivity in organic solvents. In an organic solvent in which the dielectric constant is lower than water, the ionization equilibria would be shifted:

$$HAn \xleftarrow{\text{low dielectric solvents}} H^+ + An^- \quad (13)$$

$$AH^+ \xrightarrow{\text{low dielectric solvents}} H^+ + A^0 \quad (14)$$

For acridine bases, 50:50 ethanol:water weakens the aqueous pK_a by 1.41 pH units. For the counter-acid, HAn, pK_a weakening is greater than for the protonated base, A^0H^+, because of the greater solubility of HAn in the organic phase and the production of two charges upon ionization. The net effect of organic solvent weakening is to reduce the pK_a difference between the counter-acid and the weak base. This lowers the salt-forming reactive potential. Therefore, in a given organic solvent, if salt formation fails to occur for a particular aqueous ΔpK_a, it is unlikely that salts can be formed in this organic solvent with a smaller aqueous ΔpK_a.

VARYING SALT PROPERTIES USING COUNTER-ACID GROUPINGS

For weak bases, salt-forming counter-acids can be used to alter an API's solubility, dissolution, hygroscopicity, stability, and processing.[6] Table 38-2 shows counter-acids organized into different functional groups. For each counter-acid, both the pK_a and the log P is given where appropriate. A starting point for salt expansion must begin with the properties of A^0. If, for a weak base, $\Delta pK_a = pK_{a\ A^0} - pK_{a\ \text{counter-acid, } HAn} > 0$, then aqueous salts may be possible. Use of this table and the influence of different counter-acids are covered under *Decision-Tree, Goal-Oriented Approach*, page 712.

CRYSTAL FORMATION REQUIREMENTS

In general, crystalline solids, including salts, make the most promising APIs. The amorphous form of the solid state is usually not as stable as crystals, either physically or chemically. Crystal formation is a special characteristic of a solid in which the molecules self-organize into regular, repeating, molecular patterns. Solvents play at least three roles in crystallization.

1. They provide some solubilizing capacity so that concentrated solutions can be formed.
2. They promote the nucleation process. Nucleation may be from a pure solution (homogeneous nucleation) or from a seed crystal (heterogeneous nucleation). If a solvent binds too strongly to the molecular organizing functionalities of the salt or seed crystal, crystallization will be impeded. Finding appropriate solvents for crystal formation is a very important step in salt expansion. Failure to adequately explore and find solvents that can crystallize salts could mean that very usable salts would not be evaluated in the salt-selection step because they were not synthesized.

3. Solvents, temperature, and cooling rate can impact the crystal-packing pattern of crystals. Stable polymorphic forms usually are desired for APIs. Metastable forms are normally avoided in an API because they are prone to physical and chemical instability. Solvent conditions that promote metastable and stable crystal formations will be explored under *Metastable Polymorph Formation*, page 710.

Salt Selection: Choosing the "Best" API

Salt selection is the first important API decision from the development perspective. Once a salt is chosen, time-consuming and lengthy toxicological studies are initiated that would have to be repeated if the salt form is changed. This decision involves choosing a solid-state phase, $_jA$, which balances potentially conflicting needs: increasing absorption versus maintaining an API that is consistent and can be manufactured in a market-image dosage form (see *Compressibility and Compactibility*, page 712). Figure 38-6 shows some of the factors involved in this decision.

Permeability, solubility (C_S), and pK_a are intrinsic properties of A^0 that have been already determined in the analog selection phase (see Fig 38-4). The major dependent variables, absorption and consistency of the API, can be manipulated and balanced in salt selection. In the following sections, the impact of dissolution and particle size on absorption will be explored. In addition, the consistency of the API solid state under the influence of environmental destabilizing factors—such as exposure time (t), ultraviolet light (UV), pH, moisture (H_2O), temperature (T), and pharmaceutical processing operations like milling, compression, and compaction—will be considered.

ABSORPTION ASSESSMENT

Oral absorption is generally viewed as two-step, sequential process:

$$A_{solid} \xrightarrow{\text{dissolution}} a_{GI\ tract} \xrightarrow{\text{permeation}} a_{blood} \qquad (15)$$

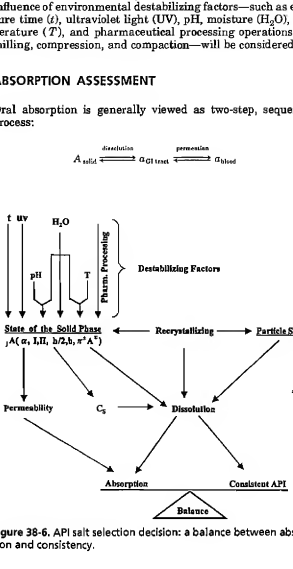

Figure 38-6. API salt selection decision: a balance between absorption and consistency.

Either dissolution of solid drug, A_{solid}, after the dosage form disintegrates in the GI tract, or the permeation of the dissolved drug, $a_{GI\ tract}$, through the GI membrane could be the slowest process. The slower of these two steps determines the overall rate of absorption and is thus rate-limiting.

Dissolution-limited absorption occurs when the rate of appearance in the GI tract by dissolution (a_{GI}) is slower than the rate of appearance in the systemic system (a_{blood}); *permeation-limited* absorption occurs when the a_{blood} appearance is the slowest process. The impact of these two rate processes on *in vitro–in vivo* (IVIV) correlations will be discussed in the section *Biopharmaceutical Classification of API*, page 714. Dissolution-limited absorption will now be considered.

The rate of dissolution of a particle is given by the Noyes–Whitney equation,

$$dA/dt = k_d S_a\,[C_S - C_{bulk}] \text{ (non-sink conditions)} \qquad (16)$$

where

A is the amount of drug dissolved.
dA/dt is the rate of dissolution (Q sometimes is used for this rate).
k_d is the intrinsic dissolution constant for the drug.
S_a is the total surface area of the dissolving particle.
C_S is the saturation solubility of the drug at the surface of the particle.
C_{bulk} is the concentration of the drug in the bulk solution.

Because the rate of dissolution depends on the concentration difference between C_S and C_{bulk}, the maximum rate of dissolution would occur if $C_{bulk} = 0$ (ie, if drug was removed from solution as fast as it dissolved). This would be analogous to a sink that could drain the water coming out of a water faucet as fast as it comes in so that the water level never built up. This analogy is the basis for referring to Equation 16 as nonsink conditions for dissolution, because drug does build up in the solution and the rate of dissolution is correspondingly reduced.

The expression for the maximum dissolution rate is found by setting C_{bulk} equal to 0:[7]

$$dA/dt = k_d S_a\, C_S \text{ (sink conditions)} \qquad (17)$$

This initial rate of the Noyes–Whitney equation is termed sink conditions for the dissolution rate.

Particle-Size Effects—For a spherical drug particle of radius r, amount m, and of density ρ, Equation 17 can be rewritten as

$$dA/dt = (3k_d m/\rho)\,(1/r)\,C_S \qquad (18)$$

This expression emphasizes the inverse relationship between the dissolution rate, dA/dt, and the particle size r, assuming no dissolution rate-reducing factors are present such as adsorbed air bubbles or aggregated particles.

Smaller particles dissolve faster than larger particles. Thus milling, a pharmaceutical unit-operation, increases dissolution because the API particle size is reduced. On the other hand, when drug particles are suspended in an aqueous solution, particles can increase in size due to recrystallization growth[8] (Fig 38-7). Dosing such suspension orally would be expected to reduce absorption because of a reduction in the dissolution rate.

Reactive Media 1: Implications for Salts of Weak Acids and Weak Bases—When a drug reacts with gastric fluids, its dissolution deviates from Equation 17. For dissolution in 0.1 N HCl, acid–base reactivity is most important for salts of weak acids and for free bases. It has been found that the low pH environment of the stomach dissolves a salt of a weak acid 10 to 100 times faster than the weak acid itself.[9] On the other hand, it is the free base, and not its HCl salt, that dissolves faster in this same environment.[10] These deviations from Equation 17 have been shown to be due to differences between bulk-solution pHs and the pH at the surface of the drug particle. Thus, Equation 17 becomes

$$dA/dt = k_d S_a\, C_{SA\text{-}0} \qquad (19)$$

EXHIBIT B

ELSEVIER

Advanced Drug Delivery Reviews 56 (2004) 335–347

Advanced
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Drug polymorphism and dosage form design: a practical perspective

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Abstract

Formulators are charged with the responsibility to formulate a product which is physically and chemically stable, manufacturable, and bioavailable. Most drugs exhibit structural polymorphism, and it is preferable to develop the most thermodynamically stable polymorph of the drug to assure reproducible bioavailability of the product over its shelf life under a variety of real-world storage conditions. There are occasional situations in which the development of a metastable crystalline or amorphous form is justified because a medical benefit is achieved. Such situations include those in which a faster dissolution rate or higher concentration are desired, in order to achieve rapid absorption and efficacy, or to achieve acceptable systemic exposure for a low-solubility drug. Another such situation is one in which the drug remains amorphous despite extensive efforts to crystallize it. If there is no particular medical benefit, there is less justification for accepting the risks of intentional development of a metastable crystalline or amorphous form. Whether or not there is medical benefit, the risks associated with development of a metastable form must be mitigated by laboratory work which provides assurance that (a) the largest possible form change will have no substantive effect on product quality or bioavailability, and/or (b) a change will not occur under all reasonable real-world storage conditions, and/or (c) analytical methodology and sampling procedures are in place which assure that a problem will be detected before dosage forms which have compromised quality or bioavailability can reach patients.

Keywords: Amorphism; Dissolution; Polymorphism; Dosage form; Bioavailability; Stability; Mechanical properties

Contents

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1. Introduction

The subject of drug polymorphism has received extensive academic and industrial attention since the early pioneering reports of Aguiar and colleagues at Parke-Davis, in which effects of polymorphism on dissolution and bioavailability were highlighted for chloramphenicol palmitate [1,2]. Drug polymorphism has been the subject of hundreds of publications and numerous excellent reviews. For both an overview and an in-depth analysis of this complex field, see the excellent series of reviews in Volume 48 (2001) of *Advanced Drug Delivery Reviews* [4–9], in "Polymorphism in Pharmaceutical Sciences" edited by Brittain [10–19], and in "Solid State Chemistry of Drugs" by Byrn et al. [20]. In addition, two very clear reviews/commentaries from the regulatory perspective have appeared [21,22].

At this point in time, it would be difficult to say anything novel about the effects of polymorphism on physical stability, chemical stability, manufacturability, or oral absorption that has not been reviewed in the references quoted above. In many respects, the 1969 review by Haleblian and McCrone was prescient in its broad coverage of the issues of polymorphism in pharmaceuticals [23]. In this article, we make no effort to review once again the vast literature on drug polymorphism. Furthermore, we do not here discuss theoretical or experimental details of the study of polymorphism. Rather, we attempt to provide a practical perspective on the impact of polymorphism on chemical stability, manufacturability, and bioavailability, with particular attention to a limited number of illustrative cases from our experience and the literature. Such a practical perspective must involve generalizations for which there are occasional exceptions.

2. Why develop multiple polymorphs?

It is generally accepted that, during the course of development of a drug, the lowest energy crystalline polymorph should be identified and chosen for development. This is critically important because the post-approval appearance of a polymorph with lower energy than the marketed polymorph can be catastrophic, as happened with the HIV protease inhibitor ritonavir [24]. For this reason, innovator pharmaceutical companies expend significant resources on this technical issue early in the development of a new drug. When executed carefully, the search for the lowest energy polymorph is arduous and time-consuming because (a) a variety of physical and chemical measurements must be made, and the stability of physical and chemical characteristics must be established in real-time storage models, (b) this search is not trivial, because a metastable polymorph may masquerade as the most stable form, and (c) every compound is different (i.e. the identity and properties of polymorphs are not theoretically predictable at present). The search for drug polymorphs is a complex empirical exercise, although recent advances in automation promise to make this activity somewhat less labor intensive.

There are three exceptions to the dictum that only the most stable polymorph should be developed. The first is extremely rare: the situation in which the lowest energy polymorph is chemically unstable due to the juxtaposition of two reactive groups in adjacent molecules in the crystal lattice. Such a "topochemical" reaction can in principle be avoided by identification of a crystalline polymorph in which the reactive species are no longer spatially close and/or oriented in a manner conducive to reaction. We are unaware of any examples of this phenomenon in

marketed drugs. The second exception is becoming more common, that is, the case of a drug whose absorption is solubility-limited and thus cannot achieve the systemic exposure required for therapy. In this case, a more soluble form of the drug is desired to deliver the therapeutic dose. The third exception is the situation in which it is desired to increase the dissolution rate of a drug to shorten T_{max} and/or increase C_{max} in order to bring quick relief for acute symptoms.

In the authors' opinion, when confronted with low solubility or the desire to decrease T_{max} or increase C_{max}, it is generally more productive to develop a stabilized amorphous form than a metastable crystalline polymorph. This will be discussed in more detail below.

In each of these three exceptions, a metastable polymorph or amorphous form is developed to provide a medical benefit.

If there is a desire to develop a metastable polymorph or amorphous form for a reason which does not provide a medical benefit, e.g. for manufacturing ease or for some other business reason, then the developer must assure that there is no significant risk to the patient. A rigorous laboratory-based analysis of the risks involved must be undertaken. This is of course also true when there is a medical benefit. In the sections below, we discuss the issues involved in the development of metastable polymorphs and amorphous forms, and their potential practical significance.

3. Chemical stability of polymorphs and amorphous forms

The polymorphs (or pseudopolymorphs) of some drugs have been shown to exhibit different chemical stability. Examples are carbamezepine [25], paroxetine maleate [26], indomethacin [27], methylprednisolone [28], furosemide [29], and enalapril maleate [30]. For example, the photodecay of form II of carbamezepine was 5- and 1.5-fold faster than forms I and III, respectively [25]. In addition to a change in the rate of decay, polymorphism may also affect the mechanism of decay, as observed in the reactivity of different polymorphs of cinnamic acid derivatives [31].

It is generally observed that the more thermodynamically stable polymorph is more chemically stable than a metastable polymorph. This has generally been attributed to higher crystal packing density of the thermodynamically favored polymorph (i.e., the "density rule"), but recent investigation suggests that other factors, such as optimized orientation of molecules, and H-bonds and non-hydrogen bonds in the crystal lattice play a more important role. Relatively small changes in crystal packing may lead to significant differences in the crystal packing density and chemical reactivity of two polymorphs, as indomethacin polymorphs [27]. Indomethacin can exist as the metastable α-form and thermodynamically favored γ-form. As an exception to the density rule, the density of metastable α-form (1.42 g/mL) is higher than that of the γ-form (1.37 g/mL), suggesting tighter packing of the less stable polymorph. Although the metastable α-form has higher density, the α-form rapidly reacts with ammonia vapor while the γ-form is inert to ammonia. The lack in correlation between higher packing density and lower reactivity of the indomethacin polymorphs is due to the differences in crystal packing/hydrogen bonding. Higher density of the α-form is due to the presence of one extra H-bond in the crystal lattice. The differences in H-bonding and the crystal packing (two centrosymmetric carboxylic groups in α-form vs. three asymmetric molecules in γ-form) leads to a layer motif in the α-form that exposes the reactive carboxylic acid group to the crystal face, while in the γ-form, H-bonded carboxylic acid groups are buried in a hydrophobic cage. Easy accessibility of the reactive carboxylic acid groups in the α-form combined with the weak H-bond of one carboxylic acid group leads to higher reactivity of the α-form [27].

The intrinsic difference in chemical stability between two polymorphs, e.g. α- and γ-indomethacin, cannot be overcome, but a less chemically stable polymorph can often be formulated in a way which results in acceptable shelf-life.

In comparison to crystalline polymorphs, the amorphous form of a drug is generally expected to be less chemically stable due to the lack of a three dimensional crystalline lattice, higher free volume and greater molecular mobility. The chemical stability of amorphous systems has been discussed in detail elsewhere [20,32–35]. As early as 1965, amorphous penicillin G was shown to be less stable than the crystalline sodium and potassium salts [36]. Physical

change of amorphous molecules from a glassy state (at $T<T_g$) to a more mobile supercooled liquid state (at $T>T_g$) may further decrease chemical stability. For example, Asn-hexapeptide was found to be 10–100-fold more stable in the glassy state compared to its supercooled liquid state [37,38]. In addition to higher reactivity, the mechanism of degradation may be different in crystalline versus disordered materials. For example, methyl transfer was the major reaction pathway in unmilled crystalline tetraglycine methyl ester (TGME), while polycondensation was the major reaction pathway in milled TGME [39]. This change in mechanism from methyl transfer to polycondensation upon milling may be due to the creation of a disordered state with higher free volume where molecules can undergo the much higher change in orientation that is needed for the polycondensation reaction [39].

It should be pointed out that a major portion of any formulation effort is the choice of excipients and processes which minimize the chemical instability of the drug. If a metastable polymorph (or amorphous form) is less chemically stable than the lowest energy form of the drug, then in many cases it will be possible to maximize the chemical stability of this metastable form through judicious formulation decisions [40–45]. Thus reduced chemical stability of a metastable crystalline or amorphous drug form does not necessarily preclude its development as a product.

For a more in-depth review of chemical stability and drug physical state, see Byrn et al. [9,20].

4. Mechanical properties of polymorphs and amorphous drug forms

Polymorphism can affect the mechanical properties of drug particles, and thus may impact the manufacturability and physical attributes of tablets. For example, polymorphs of metoprolol tartrate [46], paracetamol [47–50], sulfamerazine [51], phenobarbitone [52], carbamazepine [53,54], phenylbutazone [55] and other drugs have been shown to exhibit different mechanical properties. A common effect of polymorphism is alteration of powder flow due to the difference in particle morphology of two polymorphs. Polymorphs with needle- or rod-shaped particles may have poor flow compared to polymorphs with low aspect ratio, e.g. cubic habit or irregular spheres. The effect of polymorphism on other mechanical properties, such as hardness, yield pressure, elasticity, compressibility and bonding strength is more complex.

A simple general rule, although semi-empirical, proposed more than 20 years ago by Summers et al. can be used to predict the effect of crystal packing of polymorphs on their compressibility and bonding strength [55,56]. The more stable polymorph, due to its higher packing density, is expected to form stronger interparticle bonds but is harder to deform [46,55,56]. Since an increase in the bonding surface area resulting from deformation of particles may have higher impact on tablet strength than interparticle bond strength, the more stable of two polymorphs may provide weaker tablets. The mechanical properties of two enantiotropic polymorphs of metoprolol tartrate, metastable form I and the more stable form II (at room temperature), are consistent with this rule [46]. The porosity of pure drug tablets and yield pressure for form I were lower than for form II, suggesting that the less dense metastable form I may have less strength in the crystal lattice and be easier to deform. Form I also had higher elastic recovery, probably due to higher elasticity of form I and/or lower porosity of the tablets. As predicted, the tablets of the metastable form I were stronger at low pressures than those of form II, probably due to the higher compressibility of form I.

Factors other than those accounted for by the general rule proposed by Summers et al. may also affect the mechanical properties of two polymorphs. For example, the presence of slip planes in form I of sulfamerazine was found to be the reason for its higher plasticity than form II, the more stable form at room temperature [51]. This higher plasticity results in greater compressibility and tabletability. The authors of this study generalized this observation and suggested that crystals with slip planes would be expected to have superior tableting performance [51]. Recently, a fundamental atom–atom potential model simulation was used to predict a few mechanical properties of sulfathiazole and carbamezepine polymorphs [53]. More fundamental research in this area will improve our ability to predict the effect of polymorphism on mechanical properties.

For amorphous drug forms, mechanical properties may be different from those of crystalline drug due to

the absence of long range packing. The mechanical attributes of amorphous forms are less well understood than those of crystalline polymorphs. The lack of information on mechanical properties of amorphous drugs may be due to the physical and chemical instability of these forms, leading to reluctance in developing an amorphous form for a commercial drug product. Thus, an evaluation of mechanical properties of amorphous drugs is not routinely investigated in the pharmaceutical industry. One report comparing the mechanical properties of crystalline and amorphous forms of a model drug was published last year [57]. Compacts of amorphous material had higher brittleness and elasticity, and lower ductility than compacts prepared with the crystalline form.

Differences in the mechanical properties of two polymorphs or amorphous versus crystalline forms may or may not affect the manufacturability and physical attributes of tablets. For example, in the case of metoprolol tartrate, the differences in the mechanical properties of two polymorphs did not affect the bonding properties of tablets with relatively high drug loading [46]. The extent of the difference in the mechanical properties of two polymorphs, the drug loading, the robustness of each manufacturing step and the absolute value of the mechanical property undergoing change may be important parameters to consider while assessing the impact of polymorphism on manufacturability and physical attributes of tablets.

In some cases the favorable mechanical properties of one polymorph, even a metastable one, may be used to develop a more desirable process to manufacture tablets. For example, direct compression may be used to manufacture tablets with the more compressible orthorhombic form II of paracetamol instead of using more resource intensive granulation processes for monoclinic form I [47,50]. However, development of a metastable form for processing advantage should only be undertaken for drugs for which a very complete understanding exists with respect to form-dependent chemical stability, physical stability, and most importantly, bioavailability. This will typically be the case only for very old, highly studied, drugs.

As discussed above for chemical stability, manufacturability deficits of a particular polymorph may be overcome through judicious selection of excipients and processes. If a stable polymorph has problematic mechanical properties, this certainly does not preclude its development. It is much more preferable to use excipients and processing to overcome the mechanical deficits of a stable polymorph than to develop an unstable polymorph because of its better mechanical properties.

For a review of the effects of processing (e.g. tableting) on drug form, see Morris et al. [8] and Brittain and Fiese [17]. For a discussion of the use of excipients to compensate for the physical properties of drugs in formulations, see Amidon [58].

5. Bioavailability of polymorphs

There are many reports of polymorph-dependent bioavailability and/or absorption rate, with much of this work done in animals. See for example animal studies of chloramphenicol palmitate [59], phenylbutazone [60], amobarbitol [61], cimetidine [62], 6-mercaptopurine [63], and chlortetracycline [64]. For the purpose of the present analysis, we consider only human studies in detail.

5.1. Effects of polymorphism on dissolution and oral drug absorption in humans

Among the best known cases involving human dosing are those of chloramphenicol palmitate, mefenamic acid, oxytetracycline, and carbamazepine. These observations are quite old, having been reported in the 1950s and 1960s. For example, Aguiar et al. [1] demonstrated that absorption of chloramphenicol palmitate polymorph B was significantly greater than absorption of polymorph A in humans. Peak chloramphenicol serum levels were linearly proportional to the percentage of Form B in Form A/Form B mixtures. Chloramphenicol palmitate is a prodrug of chloramphenicol, which was prepared to provide a tasteless derivative [65]. Glazko et al. [66] reported that chloramphenicol palmitate must be hydrolyzed by intestinal esterases before the drug could be absorbed. Aguiar and colleagues demonstrated that in vitro hydrolysis of this prodrug by pancreatin was polymorph dependent, with significant hydrolysis of polymorph B and little hydrolysis of polymorph A. Aguiar and Zelmer [2] demonstrated that Form B dissolves faster than Form A, and has a much higher

solubility. This solubility difference probably results in the difference in ester hydrolysis rates, and ultimately the difference in oral absorption.

Aguiar and Zelmer [2] also reported on human absorption of two polymorphs of mefenamic acid. In this case, the two polymorphs gave almost identical blood levels. Aguiar and Zelmer calculated a free energy difference (ΔG_T) of -251 cal/mol between the two mefenamic acid polymorphs, where

$$\Delta G_T = RT \ln (\text{Solubility A}/\text{Solubility B})$$

In a similar manner, they calculated a free energy difference of -774 cal/mol between polymorphs A and B of chloramphenicol palmitate. These authors pointed out the correlation between the free energy difference and the observation of a polymorph-derived bioavailability difference (seen for chloramphenicol palmitate but not for mefenamic acid). However, the situation is clearly complicated by the issue of hydrolysis of the palmitate moiety in the lumen for chloramphenicol palmitate.

Brice and Hammer [67] reported in 1969 that oral dosing of 16 lots of oxytetracycline capsules from 13 suppliers gave drug blood levels which were lower than the innovator product. Seven of the lots gave oxytetracycline blood levels which were lower than the generally accepted minimum therapeutic level. Blood levels were generally correlated with in vitro dissolution rate. Groves subsequently reported large differences in in vitro dissolution performance of oxytetracycline tablets from various sources [68]. These studies made no attempt to relate dissolution observations to oxytetracycline polymorphism, and the observed differences may have resulted from differing formulations rather than differing polymorphs. Recently, Liebenberg et al. [69] compared six bulk oxytetracycline samples which met USP specifications, and noted that four of these contained one polymorph while the other two contained a different polymorph (form A). Tablets prepared from the form A polymorph dissolved significantly more slowly than the others in 0.1 M HCl. For example, the form A tablets exhibited ~ 55% dissolution at 30 min, while the others exhibited complete (~ 95%) dissolution at 30 min.

The drug carbamazepine exhibits polymorphism and product-to-product dissolution and bioavailability differences, but a connection between these phenomena has not been directly experimentally demonstrated. Kahela et al. [70] reported that the anhydrous and dihydrate forms of carbamazepine exhibited very similar pharmacokinetics in humans. While the anhydrous form exhibited slower in vitro dissolution than the dihydrate in 0.1 M HCl, inclusion of 0.01% polysorbate 80 in the dissolution medium essentially eliminated this difference. Another study by Jumaa-as et al. [71] demonstrated no difference in bioavailability between a generic carbamazepine product and the innovator product. Regardless, carbamazepine therapy with some products has been reported to be problematic [72,73]. Meyer et al. [74] reported on in vitro/in vivo studies of three out of 53 batches of generic carbamazepine tablets which were recalled due to clinical failures and dissolution changes. In vitro dissolution testing, carried out in water containing 1% sodium lauryl sulfate, revealed that two of the batches dissolved more slowly than the innovator product, and one batch dissolved more quickly. While the innovator product gave ~ 95% dissolution in 90 min in this medium, the slower generic batches gave ~ 35% and 75% dissolution. In humans, the generic batches gave mean relative AUCs (relative to the innovator) of 60–113%, with the same rank order observed in the in vitro dissolution behavior. It was suggested that moisture uptake during storage and particle size differences may have been involved in the irreproducible behavior of the generic tablets of this practically insoluble drug. It is known that anhydrous carbamazepine converts to the dihydrate quickly, e.g. completely within 1 h, when the anhydrous form is suspended in water [75].

The mechanistic uncertainty in these examples (i.e. whether drug physical form was involved in the observed dissolution or bioavailability differences) results from the lack of spectroscopic data which can identify the drug polymorph in a complex dosage form. Modern techniques such as ss-NMR and NIR can identify polymorphs in dosage forms (within limits), and should facilitate increased mechanistic understanding in future studies.

It is clear that for some drugs, there will be polymorph-dependent bioavailability. For a larger group, there will be polymorph-dependent absorption rate, reflected in in vivo C_{max}. For some pairs of polymorphs, there will be pharmacokinetic bioequi-

valence. As described above, in 1969 Aguiar and Zelmer proposed that polymorphs with a large free energy difference between them are likely to differ in pharmacokinetic behavior. This simply reflects a difference in solubility. In addition, polymorphs may exhibit different dissolution rates because of their different crystal habits, and this may also contribute to in vivo absorption rate differences.

For an excellent in-depth review of the relationships between polymorphism and solubility and dissolution rate, see Brittain and Grant [16].

5.2. The role of dose in bioavailability of high energy polymorphs

A significant solubility difference between two polymorphs is likely to result in a difference in oral absorption rate, reflected in a difference in C_{max}. Differences in AUC, or oral bioavailability, will occur less often, and will depend upon the same underlying principles which govern the bioavailability differences between two unrelated drugs. Drug absorption may be modeled in a variety of ways [76,77]. A simple context in which to discuss this issue is provided by the concept of the maximum absorbable dose (MAD) [3,78]. The MAD is a conceptual tool which represents the quantity of drug which could be absorbed if the small intestine could be saturated with drug for 4.5 h (270 min), the average small intestinal transit time.

$$\mathrm{MAD} = S \times K_a \times \mathrm{SIWV} \times \mathrm{SITT}$$

S, solubility (mg/ml) at pH 6.5; K_a, transintestinal absorption rate constant (min^{-1}); SIWV, small intestinal water volume (ml); SITT, small intestinal transit time (min).

The solubility at pH 6.5 reflects the solubility in the small intestine. K_a is determined in a rat intestinal perfusion experiment. In our laboratories, it has been observed that the human K_a is 1.4 times the rat K_a [79]. SIWV is the amount of water available for dissolution, generally accepted to be ~ 250 ml. While SIWV and SITT are approximations, moderate variations in these parameters do not significantly affect this analysis. The resulting MAD is in mg. This analysis ignores first pass intestinal and hepatic metabolism, which can be saturated, thus affecting bioavailability.

Table 1
MAD

Rat K_a (min^{-1}) [Human K_a]	Solubility (mg/ml)	MAD (mg) (Human)
0.003 [0.004]	0.01	2.7
0.003 [0.004]	0.02	5.4
0.003 [0.004]	0.03	8.1
0.03 [0.04]	0.01	27
0.03 [0.04]	0.02	54
0.03 [0.04]	0.03	81

If the intent is to increase bioavailability, it can be readily seen that increasing drug solubility will result in increased MAD (Table 1). In general, the range of solubility differences between polymorphs is typically 2–3-fold, due to the relatively small difference in free energy between polymorphs. Thus a higher energy polymorph with a solubility which is 3 × that of the lowest energy polymorph may give a systemic exposure which is 3 × that given by the low energy polymorph. As shown in Table 1, for a low human K_a of 0.004 min^{-1}, and a solubility of 0.01 mg/ml, a 3-fold increase in solubility only results in a MAD of 8.1 mg, which would be inadequate if the desired absorbed dose were, say, 50 mg. If bioavailability were practically governed in this way, there would not be much opportunity to increase the bioavailability of low-solubility drugs by developing a high energy polymorph or amorphous form.

In fact, equilibrium solubility may not be very relevant for oral absorption enhancement if polymorphs (or pseudopolymorphs) are physically unstable in the aqueous environment. Instead, intrinsic dissolution rate (IDR) and kinetic solubility over 4–6 h may be more relevant parameters to consider while studying the oral absorption of polymorphs. Form changes may sometimes occur during IDR and kinetic solubility measurements, but these changes are occurring on a timescale relevant for oral absorption, i.e. the small intestinal transit time. The kinetic solubility of a metastable polymorph over 4–6 h is often higher than its equilibrium solubility. The rank order of the IDR of polymorphs has been found to correlate well with the rank order for oral absorption due to the faster rate of dissolution of the less stable polymorph, leading to higher concentration of drug in solution available for absorption. Generally, this may

lead to a higher in vivo C_{max}, but not a higher AUC, unless the drug is present in suspension throughout its small intestinal transit time (i.e. the dose is substantially greater than the MAD calculated for the thermodynamically stable polymorph). In some circumstances, the IDR and the achievable metastable supersaturation may temporarily provide a maximum drug concentration in the intestinal lumen which is in excess of the equilibrium solubility of the high energy polymorph. If the drug does not rapidly precipitate in the GI lumen, then the achievable MAD can conceivably be very large.

Although IDR may be a good single parameter to describe relative dissolution rates of two polymorphs, this does not take into account other factors that may govern oral absorption, namely, rate of conversion of one polymorph to another less soluble polymorph in the GI lumen, and the resulting precipitation of drug in the GI fluid. It is generally not possible to theoretically predict the degree of supersaturation of drug from a metastable polymorph or amorphous form, or the kinetics of physical conversion of one polymorph to another. However, these processes may be quantified by comparing the extent of supersaturation in model GI fluid according to Eq. (1), and more importantly Eq. (2):

Supersaturated concentration ratio (SCR)

$$= C_{\text{max. form 1}}/C_{\text{max. form 2}} \quad (1)$$

Supersaturated AUC ratio (SAR)

$$= \text{AUC}_{\text{form 1}}/\text{AUC}_{\text{form 2}} \quad (2)$$

where $C_{\text{max, form 1}}$ and $C_{\text{max. form 2}}$ are the in vitro maximum concentrations of drug in solution from forms 1 and 2, respectively; and $\text{AUC}_{\text{form 1}}$ and $\text{AUC}_{\text{form 2}}$ are the areas under the in vitro drug concentration versus time curve over, say, 6 h, for forms 1 and 2, respectively. If a high dose (in substantial excess of the MAD for the stable polymorph) is dosed, and supersaturation is maintained for a long time, e.g. 6 h, while drug is absorbed, then the potential exists to achieve absorption of an amount of drug much higher than the MAD for the stable polymorph.

The greatest effect of dissolution rate and supersaturation of drug from a polymorph or amorphous form is expected for compounds with high permeability and low solubility relative to dose (i.e. BCS class II compounds, where the administered dose will remain as a suspension for most of the absorption period). For solutes where the dose is expected to be very soluble in the GI fluid (i.e. BCS class I and III compounds) there may be no, or minimal differences in the AUC of polymorphs because solubility is not expected to be rate limiting in oral absorption.

5.3. Potential effects of physical instability of a metastable polymorph on oral absorption

Developing a bioequivalent product with a metastable form may not be easy, but in some cases it may be possible using formulation methods to achieve a bioequivalent AUC. It may be trickier, but possible, to blunt the higher pharmacokinetic C_{max} which results from the higher dissolution rate of the metastable form. Thus, it may be possible to develop a formulation with a metastable drug form which is bioequivalent to the innovator formulation containing the thermodynamically most stable form. For some drugs, there is a potential danger that bioavailability could be lost if the metastable form converts to the more stable form during the shelf-life of the product. This is illustrated in Table 2. A metastable drug form may be formulated in a product (e.g. tablet) which has the same dissolution rate (Y) as a formulation of the stable drug form. Of course the metastable drug product will have to be formulated in a way which slows the drug dissolution rate. If the metastable form converts to the stable form in the product on storage, then the dissolution rate may decrease and in vivo performance may be compromised. This compromised in vivo performance may involve increased pharmacokinetic

Table 2
Potential performance changes on storage of a dosage form containing a metastable drug form

Drug form in formulation	IDR	Dissolution rate in formulated product	Dissolution rate in product after storage if metastable form converts to stable form
Metastable	$X+\Delta X$	Y	$Y-\Delta Y$
Stable	X	Y	Y

variability and, more extremely, decreased C_{max} and bioavailability.

As an example, phenylbutazone Form C exhibits a dissolution rate and solubility which are 1.5× and 1.2× that of Form A, respectively [80]. On storage at 40 °C for 12 months, Form C was converted to 60% Form A. As another example, various marketed tablet formulations of glibenclamide have been shown to exhibit differing in vitro dissolution [81]. Glibenclamide exhibits forms which differ greater than 10-fold in solubility in simulated gastric fluid [82]. However, for glibenclamide the connection between product-to-product variability and polymorphism has not been directly demonstrated, but provides a possible explanation.

6. Dosage form decision

6.1. Metastable crystalline polymorph versus amorphous form

As discussed above, metastable crystalline polymorphs and amorphous forms may be less chemically stable and potentially possess different (in some cases less desirable) mechanical properties than the related stable crystalline form. These potential problems can in theory be solved by judicious choice of excipients and appropriate formulation strategies. In addition to chemical instability and mechanical properties, physical stability of the drug during product shelf life is of paramount importance in developing a drug product. A change in physical form can not only affect chemical stability and mechanical attributes of tablets, but much more importantly can compromise the oral absorption of a drug via a change in solubility.

Physical stabilization of intrinsically physically unstable crystalline polymorphs is a challenge because, by definition, the use of additives for improvement of physical stability involves a two phase system (polymorph and stabilizer) where the drug molecules are not in intimate contact with the stabilizer. Furthermore, physical conversion can be relatively precipitous, and exceptional care must be taken to design stability studies which cover all reasonable real-world conditions which such a formulation may encounter (e.g. temperature cycling). There is a need for increased understanding of stabilization of metastable crystalline forms, and research in this area is sorely needed if practical solutions are to be found.

Amorphous forms are of course also physically unstable. For an introduction to the literature and general concepts on the physical stability of amorphous forms see Yu [5], Yoshioka et al. [83], and Crowley and Zografi [84]. Physical stabilization of amorphous forms is possible in some situations by generating intimate contact between the amorphous drug and the stabilizer by creating a drug/stabilizer dispersion [85–88]. The use of such dispersions, particularly with polymers, to intentionally enhance drug solubility has been known for many years [89,90], and practical formulations which achieve facile low-solubility drug dissolution and supersaturation have recently been described [91,92]. The identification of pharmaceutically acceptable stabilizers and processes which can inhibit solid state crystallization for a reasonable shelf-life is also a recent development [86].

While stabilized amorphous forms can sometimes be developed for intentional bioavailability improvement, the use of such forms to provide a dosage form which is bioequivalent to the stable drug crystalline form would be difficult, but perhaps possible in certain situations.

7. Solvates and hydrates

In general, the analysis provided above for the behavior of polymorphs also applies to metastable solvates and hydrates. For example, the dissolution rate and solubility of a drug can differ significantly for different solvates. Glibenclamide has been isolated as pentanol and toluene solvates, and these solvates exhibit higher solubility and dissolution rate than two non-solvated polymorphs [93]. In formulation of solvates (other than hydrates), the formulator must be careful to address the toxicity of the associated solvent, and carefully evaluate interactions of the drug and mobile solvent molecules with excipients on storage, which may result in compromised performance.

Similar to polymorphs in general, the physical stability of hydrates and anhydrous forms may depend upon the relative humidity and/or temperature of the environment, and the most stable form may switch as

the humidity/temperature is varied. Anhydrous to hydrate transitions can occur during dissolution at the drug/medium interface and can affect dissolution rate and perhaps bioavailability. Discussion of these issues is beyond the intended scope of this review.

Pharmaceutical solvates and hydrates have been reviewed by Morris [13], and hydrates have been reviewed by Khankari and Grant [94].

8. Conclusions

In principle, any polymorph or hydrate/solvate or amorphous form of a drug can be appropriately formulated. In practice, for some drugs constraints may be encountered. In general, the following conclusions are drawn from the literature and the experience of the authors:

1. It is always advisable to identify the lowest energy crystalline polymorph of a drug candidate during development, and to develop this form. While this form may not be the most processable form available, processing deficits can almost always be overcome with judicious choice of excipients and formulation processes. The lowest energy polymorph is almost always the most chemically stable form, and will not convert to another polymorph during storage as drug product. Of course, care must be taken to avoid conversion during processing to a physically metastable, perhaps chemically unstable, form.
2. Metastable crystalline polymorphs may be less chemically stable than the most physically stable crystalline form. Likewise, amorphous drug forms will generally be less chemically stable than the most physically stable form. It is often possible to improve chemical stability of such forms through judicious choice of excipients and formulation processes.
3. If a developer is precluded from developing the lowest energy drug form, for medical benefit or otherwise, it is preferable to develop a stabilized amorphous form, e.g. as a dispersion. Development of a metastable crystalline or amorphous form as a standard physical mixture or granulation with excipients is less preferable, because it is difficult to guarantee that such a formulation will resist form changes on storage. If the metastable form converts to the stable less soluble form in the dosage form on storage, then in vivo C_{max} will almost certainly decrease, and in vivo AUC may also decrease depending upon where the drug lies in dose–solubility–permeability space. However, there will be occasional exceptions in which an unstabilized amorphous or metastable crystalline polymorph will be physically stable over the shelf-life of a formulation.

In the end, the manufacturer, whether innovator or generic, must guarantee the quality and bioavailability of the dosage form. It is highly desirable that the drug physical form not change over the storage life of the drug product. If the physical form does change, or if it could change, then the manufacturer must provide assurance (a) that the largest possible change would have no substantive effect on product quality or bioavailability, and/or (b) that extensive scientific study of the formulation guarantees that a change will not occur under all reasonable real-world storage conditions, and/or (c) that analytical methodology and sampling procedures are in place which guarantee that a problem will be detected before dosage forms which have compromised quality or bioavailability can reach patients.

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no manifestations of upper tract infection (e.g., flank pain, chills, fever), no history of recurrent urinary tract infections (20% of patients in the clinical studies had a prior episode of acute cystitis within the preceding year), no known structural abnormalities, and no clinical or laboratory evidence of hepatic dysfunction, and no known or suspected CNS disorders, such as epilepsy, or other factors which would predispose to seizures. In these studies, the following clinical success (resolution of symptoms) and microbiologic eradication rates were obtained:

(See table at top of previous page).

Pathogen	Fosfomycin 3 gm single dose	Ciprofloxacin 250 mg bid × 7d	Trimethoprim/sulfamethoxazole 160 mg/800 mg bid × 10d	Nitrofurantoin 100mg bid × 7d
E. coli	509/644 (79%)	184/187 (98%)	171/174 (98%)	146/187 (78%)
S. faecalis	10/10 (100%)	0/0	4/4 (100%)	1/3 (66%)

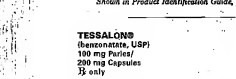
Rev. 6/02 RMC 227

Shown in Product Identification Guide, page 314

TESSALON®
(benzonatate, USP)
100 mg Perles/
200 mg Capsules
℞ only

DESCRIPTION

TESSALON, a non-narcotic oral antitussive agent, is 2, 5, 8, 11, 14, 17, 20, 29, 32-nonaoxatetratriacontyl-3[4-p-(butylamino) benzoate; with a molecular weight of 603.7.



Each TESSALON Perle contains:
Benzonatate, USP 100 mg
Each TESSALON Capsule contains:
Benzonatate, USP 200 mg
TESSALON Capsules also contain: D&C Yellow 10, gelatin, glycerin, methylparaben and propylparaben.

CLINICAL PHARMACOLOGY

TESSALON acts peripherally by anesthetizing the stretch receptors located in the respiratory passages, lungs, and pleura by dampening their activity and thereby reducing the cough reflex at its source. It begins to act within 15 to 20 minutes and its effect lasts for 3 to 8 hours. TESSALON has no inhibitory effect on the respiratory center in recommended dosage.

INDICATIONS AND USAGE

TESSALON is indicated for the symptomatic relief of cough.

CONTRAINDICATIONS

Hypersensitivity to benzonatate or related compounds.

WARNINGS

Severe hypersensitivity reactions (including bronchospasm, laryngospasm and cardiovascular collapse) have been reported which are possibly related to local anesthesia from sucking or chewing the perle instead of swallowing it. Severe reactions have required intervention with vasopressor agents and supportive measures.

Isolated instances of bizarre behavior, including mental confusion and visual hallucinations, have also been reported in patients taking TESSALON in combination with other prescribed drugs.

PRECAUTIONS

Benzonatate is chemically related to anesthetic agents of the para-amino-benzoic acid class (e.g., procaine; tetracaine) and has been associated with adverse CNS effects possibly related to prior sensitivity to related agents or interaction with concomitant medication.

Information for Patients: Release of TESSALON from the capsule in the mouth can produce a temporary local anesthesia of the oral mucosa and choking could occur. Therefore, the capsules should be swallowed without chewing.

Usage in Pregnancy: Pregnancy Category C. Animal reproduction studies have not been conducted with TESSALON. It is also not known whether TESSALON can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. TESSALON should be given to a pregnant woman only if clearly needed.

Nursing Mothers: It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk caution should be exercised when TESSALON is administered to a nursing woman.

Information will be superseded by supplements and subsequent editions

not been conducted with TESSALON.

Pediatric Use: Safety and effectiveness in children below the age of 10 has not been established.

ADVERSE REACTIONS

Potential Adverse Reactions to TESSALON may include: Hypersensitivity reactions including bronchospasm, laryngospasm, cardiovascular collapse possibly related to local anesthesia from chewing or sucking the capsule.

CNS: sedation; headache; dizziness; mental confusion; visual hallucinations.

GI: constipation, nausea, GI upset.

Dermatologic: pruritis; skin eruptions.

Other: nasal congestion; sensation of burning in the eyes; vague "chilly" sensation; numbness of the chest; hypersensitivity

Rare instances of deliberate or accidental overdose have resulted in death.

OVERDOSAGE

Overdose may result in death.

The drug is chemically related to tetracaine and other topical anesthetics and shares various aspects of their pharmacology and toxicology. Drugs of this type are generally well absorbed after ingestion.

Signs and Symptoms:

If capsules are chewed or dissolved in the mouth, oropharyngeal anesthesia will develop rapidly. CNS stimulation may cause restlessness and tremors which may proceed to clonic convulsions followed by profound CNS depression.

Treatment:

Evacuate gastric contents and administer copious amounts of activated charcoal slurry. Even in the comatose patient, cough and gag reflexes may be so depressed as to necessitate special attention to protection against aspiration of gastric contents and orally administered materials. Convulsions should be treated with a short-acting barbiturate given intravenously and carefully titrated for the smallest effective dosage. Intensive support of respiration and cardiovascular-renal function is an essential feature of the treatment of severe intoxication from overdosage.

Do not use CNS stimulants.

DOSAGE AND ADMINISTRATION

Adults and Children over 10: Usual dose is one 100 mg or 200 mg capsule t.i.d. as required. If necessary, up to 600 mg daily may be given.

HOW SUPPLIED

Perles, 100 mg (yellow); bottles of 100
NDC 0456-0698-01 Imprint: T.
Perles, 100 mg (yellow); bottles of 500
NDC 0456-0698-02 Imprint: T.
Capsules, 200 mg (yellow); bottles of 100
NDC 0456-0698-03 Imprint: 0698.
Capsules, 200 mg (yellow); bottles of 500
NDC 0456-0698-05 Imprint: 0698.
Store at 25°C (77°F); excursions permitted to 15–30°C (59–86°F) [see USP Controlled Room Temperature].
Rev. 3/03 (04)

Mfd by
Cardinal Health
St. Petersburg, Florida 33716
for
FOREST PHARMACEUTICALS, INC.
SUBSIDIARY OF FOREST LABORATORIES, INC.
ST. LOUIS, MISSOURI 63045
©2003 Forest Laboratories, Inc.

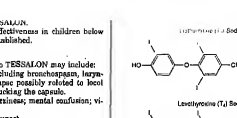
Shown in Product Identification Guide, page 314

THYROLAR® Tablets ℞
(*liy-ro-lar*)
(Liotrix Tablets, USP)

DESCRIPTION

Thyrolar Tablets (Liotrix Tablets, USP) contain triiodothyronine (T_3 liothyronine) sodium and tetraiodothyronine (T_4, levothyroxine) sodium in the amounts listed in the "How Supplied" section. (T_3 liothyronine sodium is approximately four times as potent as T_4 thyroxine on a microgram for microgram basis.)

The inactive ingredients are calcium phosphate, colloidal silicon dioxide, corn starch, lactose, and magnesium stearate. The tablets also contain the following dyes: Thyrolar $\frac{1}{2}$-FD&C Blue #1 and FD&C Red #40; Thyrolar $\frac{1}{2}$-FD&C Red #40 and D&C Yellow #10; Thyrolar 1-FD&C Red #40; Thyrolar 2-FD&C Blue #1, FD&C Red #40, and D&C Yellow #10; Thyrolar 3-FD&C Red #40 and D&C Yellow #10.



HOW SUPPLIED

Thyrolar Tablets (Liotrix Tablets, USP) are available in potencies coded as follows:
[See table below]
Supplied in bottles of 100, two-layered compressed tablets.
Tablets should be stored at cold temperature, between 2° and 40°F (2° and 8°C) in a tight, light-resistant container.
Note: (T_3 liothyronine sodium is approximately four times as potent as T_4 thyroxine on a microgram for microgram basis.)
Rev. 11/02
FOREST PHARMACEUTICALS, INC.
A Subsidiary of Forest Laboratories, Inc.
St. Louis, MO 63045
©2002 Forest Laboratories, Inc.

Shown in Product Identification Guide, page 314

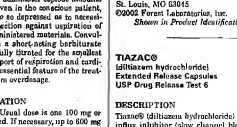
THYROLAR® Tablets

Name	Composition (T_3/T_4 per tablet)	Color	Armscode®	NDC
Thyrolar—$\frac{1}{2}$	3.1 mcg/12.5 mcg	Violet/White	YC	0456-0010-01
Thyrolar—$\frac{1}{2}$	6.25 mcg/25 mcg	Peach/White	YD	0456-0015-01
Thyrolar—1	12.5 mcg/50 mcg	Pink/White	YE	0456-0050-01
Thyrolar—2	25 mcg/100 mcg	Green/White	YF	0456-0065-01
Thyrolar—3	37.5 mcg/150 mcg	Yellow/White	YH	0456-0060-01

TIAZAC®
(diltiazem hydrochloride)
Extended Release Capsules
USP Drug Release Test 6

DESCRIPTION

Tiazac® (diltiazem hydrochloride) is a calcium ion influx inhibitor (slow channel blocker). Chemically known hydrochloride is 1,5-Benzothiazepin-4(5H)-3-(acetyloxy)-5[2-(dimethylamino)ethyl]-2, 3-dihydro-2-(4-methoxyphenyl)-, monohydrochloride, (+)-cis. The structure is:



Diltiazem hydrochloride is a white to off-white crystalline powder with a bitter taste. It is soluble in water, methanol and chloroform and has a molecular weight of 450.99. Tiazac® capsules contain diltiazem hydrochloride in two coated release beads at doses of 120, 180, 240, 300, 360 or 420 mg.

Tiazac® also contains: Microcrystalline Cellulose NF, Sucrose, Eudragit, Povidone USP, Talc USP, Magnesium Stearate NF, Hydroxypropylmethylcellulose USP, Lauryl Laurate USP, Polysorbate NF, Simethicone, Gelatin NF, FD&C Blue #1, FD&C Red #40, D&C Red #7, FD&C Green #3, Black Iron Oxide USP, and other ingredients for oral administration.

CLINICAL PHARMACOLOGY

The therapeutic effects of diltiazem hydrochloride are believed to be related to its ability to inhibit the cellular influx of calcium ions during membrane depolarization of cardiac and vascular smooth muscle.

Mechanisms of Action.

Hypertension: Diltiazem produces its antihypertensive effect primarily by relaxation of vascular smooth muscle and the resultant decrease in peripheral vascular resistance. The magnitude of blood pressure reduction is related to the degree of hypertension: thus hypertensive individuals experience an antihypertensive effect, whereas those with a modest fall in blood pressure in normotensives.

Angina: Diltiazem HCl has been shown to produce increases in exercise tolerance, probably due to its ability to reduce myocardial oxygen demand. This is accomplished

reclosable foil
aste receptacle out

emperature, 25°C (7
–86°F (15–30°C). Avoid
86°F (30°C).
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2 10/01
ation Guide, page 329

ection, USP)

(HCG), a polypeptide hor
lacenta, is composed of a
lpha sub-unit is essentially
s of the human pituitary
rmone (LH) and follicle
well as to the alpha sub-unit
hormone (TSH). The beta
er in amino acid sequence
opin for injection, USP) is a
paration obtained from the
standardized by a biological
for intramuscular injection
g 10,000 USP Units of ster
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phate. If required, pH is ad
nd/or phosphoric acid. Each
vial of solvent containing
sodium chloride and 0.9%
IS NOT FOR USE IN
is adjusted with sodium
cid.

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have a small degree of FSH
roduction of gonadal steroid
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and may stimulate testic
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reversible when HCG is dis
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mid-cycle LH surge trigger
for LH in this function.
CG secreted by the placenta
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of estrogen and progeste
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thought to induce testi
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help predict whether or
in the future. Although
ing HCG administration
the response is tem
ted in children between

lotropic hypogonadism (hy
tuitary deficiency) in mal
pregnancy in the anov
m the cause of anovulation
primary ovarian failure.
ely pretreated with h

...ICATIONS

...uberty, prostatic carcinoma or other androgen-... plasm, prior allergic reaction to HCG.

... be used in conjunction with human meno-... adotropins only by physicians experienced with ... problems who are familiar with the criteria for ... ction, contraindications, warnings, precautions, ... reactions described in the package insert for ...

... serious adverse reactions during this use are: ... hyperstimulation, a syndrome of sudden ovar-... ment, ascites with or without pain, and/or pleu-... on, (2) Rupture of ovarian cysts with resultant ... toneum, (3) Multiple births, and (4) Arterial ... bolism.

...TIONS

... ogens may cause fluid retention, HCG should be ... caution in patients with cardiac or renal disease, ... raine, or asthma.

...Use

... of androgen secretion by HCG may induce preco-... erty in pediatric patients treated for cryptorchi-... apy should be discontinued if signs of precocious ... cur.

...Use

... udies of PREGNYL® (chorionic gonadotropin for ... USP) did not include subjects aged 65 and over.

...E REACTIONS

...he, irritability, restlessness, depression, fatigue, ... recocious puberty, gynecomastia, pain at the site of ...ion.

... AND ADMINISTRATION

... uscular use only. The dosage regimen employed ... rticular case will depend upon the indication for ... the age and weight of the patient, and the physi-... ference. The following regimens have been advo-... y various authorities:

... rtal cryptorchidism not due to anatomical ob-... Therapy is usually instituted in children between ... of 4 and 9.

... USP Units three times weekly for three weeks.

... USP Units every second day for four injections.

... ections for 500 to 1,000 USP Units over a period of ... eeks.

... USP Units three times weekly for four to six weeks. ... s course of treatment is not successful, another ... is begun one month later, giving 1,000 USP Units ... jection.

... cases of hypogonadotropic hypogonadism in males.

... 1,000 USP Units three times a week for three ..., followed by the same dose twice a week for three ...

...000 USP Units three times weekly for six to nine ...onths, following which the dosage may be reduced to ...000 USP Units three times weekly for an additional ...ree months.

...ion of ovulation and pregnancy in the anovulatory, in-... woman in whom the cause of anovulation is secondary ... due to primary ovarian failure and who has been ...opriately pretreated with human menotropins. (See pre-...ing information for menotropins for dosage and admin-...tion for that drug product.)

...000 to 10,000 USP Units one day following the last dose of ...otropins. (A dosage of 10,000 USP Units is recom-...ended in the labeling for menotropins.)

...ections for Reconstitution

...vial package: Withdraw sterile air from lyophilized vial ... inject into diluent vial. Remove 1–10 mL from diluent ... add to lyophilized vial; agitate gently until powder is ...pletely dissolved in solution.

...renteral drug products should be inspected visually for ...ticulate matter and discoloration prior to administra-... whenever solution and container permit.

...PORTANT: USE COMPLETELY AFTER RECONSTITUTION. ...ECONSTITUTED SOLUTION IS STABLE FOR 60 DAYS ...HEN REFRIGERATED.

...OW SUPPLIED

...-vial package containing:

...10 mL lyophilized multiple dose vial containing: 10,000 ... Units chorionic gonadotropin per vial, NDC 0052-...5-10.

...10 mL vial of solvent containing: water for injection with ...um chloride 0.56% and benzyl alcohol 0.9%, NDC 0052-...-10.

...en reconstituted, each 10 mL vial contains:

...orionic gonadotropin	10,000 USP Units
...basic sodium phosphate	5 mg
...ic sodium phosphate	4.4 mg
...um chloride	0.56%
...zyl alcohol	0.9%

...quired pH adjusted with sodium hydroxide and/or phos-...ic acid.

...ge: Store at 15°–30°C (59°–86°F). Reconstituted solu-... is stable for 60 days when refrigerated.

...only

Manufactured by
Organon Inc.
West Orange, NJ 07052

8/98 15
5310122

REMERON® ℞
(mirtazapine) Tablets

HOW SUPPLIED

REMERON® (mirtazapine) Tablets are supplied as:

15 mg Tablets — oval, scored, yellow, coated, with "Organon" debossed on one side and "T/3" on the other side.

Bottles of 30	NDC 0052-0105-30
Bottles of 100	NDC 0052-0105-91
Unit Dose, Box of 100	NDC 0052-0105-90*

30 mg Tablets — oval, scored, red-brown, coated, with "Organon" debossed on one side and "T/5" on the other side.

Bottles of 30	NDC 0052-0107-30
Bottles of 100	NDC 0052-0107-91
Unit Dose, Box of 100	NDC 0052-0107-90*

45 mg Tablets — oval, white, coated, with "Organon" debossed on one side and "T/7" on the other side.

Bottles of 30	NDC 0052-0109-30

*Unit dose packs are provided as a blisterpack with 10 strips, each of which contains 10 tablets.

Storage

Store at 25°C (77°F); excursions permitted to 15–30°C (59–86°F) [see USP Controlled Room Temperature]. Protect from light and moisture.

℞ only

Organon

Manufactured for Organon Inc., West Orange, NJ 07052
by N.V. Organon, Oss, The Netherlands

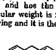
5310179 5/02 17

Shown in Product Identification Guide, page 329

REMERONSolTab® ℞
[rĕ'mər-ŏn-sŏl-tăb]
(mirtazapine)
Orally Disintegrating Tablets
Once-A-Day

DESCRIPTION

REMERONSolTab® (mirtazapine) Orally Disintegrating Tablets are an orally administered drug. Mirtazapine has a tetracyclic chemical structure and belongs to the piperazino-azepine group of compounds. It is designated 1,2,3,4,10,14b-hexahydro-2-methylpyrazino [2,1-a] pyrido [2,3-c] benzazepine and has the empirical formula of $C_{17}H_{19}N_3$. Its molecular weight is 265.36. The structural formula is the following and it is the racemic mixture:



Mirtazapine is a white to creamy white crystalline powder which is slightly soluble in water.

REMERONSolTab® is available for oral administration as an orally disintegrating tablet containing 15, 30, or 45 mg of mirtazapine. It disintegrates in the mouth within seconds after placement on the tongue allowing its contents to be subsequently swallowed with or without water. REMERONSolTab® also contains the following inactive ingredients: aspartame, citric acid, crospovidone, hydroxypropyl methylcellulose, magnesium stearate, mannitol, microcrystalline cellulose, natural and artificial orange flavor, poly-methacrylate, povidone, sodium bicarbonate, starch, sucrose.

CLINICAL PHARMACOLOGY

Pharmacodynamics

The mechanism of action of REMERONSolTab® (mirtazapine) Orally Disintegrating Tablets, as with other drugs effective in the treatment of major depressive disorder, is unknown.

Evidence gathered in preclinical studies suggests that mirtazapine enhances central noradrenergic and serotonergic activity. These studies have shown that mirtazapine acts as an antagonist at central presynaptic α_2 adrenergic inhibitory autoreceptors and heteroreceptors, an action that is postulated to result in an increase in central noradrenergic and serotonergic activity.

Mirtazapine is a potent antagonist of $5\text{-}HT_2$ and $5\text{-}HT_3$ receptors. Mirtazapine has no significant affinity for the $5\text{-}HT_{1A}$ and $5\text{-}HT_{1B}$ receptors.

Mirtazapine is a potent antagonist of histamine (H_1) receptors, a property that may explain its prominent sedative effects.

Mirtazapine is a moderate peripheral α_1 adrenergic antagonist, a property that may explain the occasional orthostatic hypotension reported in association with its use.

Mirtazapine is a moderate antagonist at muscarinic receptors, a property that may explain the relatively low incidence of anti-cholinergic side effects associated with its use.

Pharmacokinetics

REMERONSolTab® (mirtazapine) Orally Disintegrating Tablets are rapidly and completely absorbed following oral administration and have a half-life of about 20–40 hours. Peak plasma concentrations are reached within about 2 hours following an oral dose. The presence of food in the stomach has a minimal effect on both the rate and extent of absorption and does not require a dosage adjustment. REMERONSolTab® Orally Disintegrating Tablets are bioequivalent to REMERON® (mirtazapine) Tablets.

Mirtazapine is extensively metabolized after oral administration. Major pathways of biotransformation are demethylation and hydroxylation followed by glucuronide conjugation. *In vitro* data from human liver microsomes indicate that cytochrome 2D6 and 1A2 are involved in the formation of the 8-hydroxy metabolite of mirtazapine, whereas cytochrome 3A is considered to be responsible for the formation of the N-desmethyl and N-oxide metabolite. Mirtazapine has an absolute bioavailability of about 50%. It is eliminated predominantly via urine (75%) with 15% in feces. Several unconjugated metabolites possess pharmacological activity but are present in the plasma at very low levels. The (–) enantiomer has an elimination half-life that is approximately twice as long as the (+) enantiomer and therefore achieves plasma levels that are about three times as high as that of the (+) enantiomer.

Plasma levels are linearly related to dose over a dose range of 15–80 mg. The mean elimination half-life of mirtazapine after oral administration ranges from approximately 20–40 hours across age and gender subgroups, with females of all ages exhibiting significantly longer elimination half-lives than males (mean half-life of 37 hours for females vs. 26 hours for males). Steady state plasma levels of mirtazapine are attained within 5 days, with about 50% accumulation (accumulation ratio = 1.5).

Mirtazapine is approximately 85% bound to plasma proteins over a concentration range of 0.01–10 µg/mL.

Special Populations

Geriatric

Following oral administration of REMERON® (mirtazapine) Tablets 20 mg/day for 7 days to subjects of varying ages (range, 25–74), oral clearance of mirtazapine was reduced in the elderly compared to the younger subjects. The differences were most striking in males, with a 40% lower clearance in elderly males compared to younger males, while the clearance in elderly females was only 10% lower compared to younger females. Caution is indicated in administering REMERONSolTab® (mirtazapine) Orally Disintegrating Tablets to elderly patients (see PRECAUTIONS and DOSAGE AND ADMINISTRATION).

Pediatrics

Safety and effectiveness of mirtazapine in the pediatric population have not been established (see PRECAUTIONS).

Gender

The mean elimination half-life of mirtazapine after oral administration ranges from approximately 20–40 hours across age and gender subgroups, with females of all ages exhibiting significantly longer elimination half-lives than males (mean half-life of 37 hours for females vs. 26 hours for males) (see Pharmacokinetics).

Race

There have been no clinical studies to evaluate the effect of race on the pharmacokinetics of REMERONSolTab®.

Renal Insufficiency

The disposition of mirtazapine was studied in patients with varying degrees of renal function. Elimination of mirtazapine is correlated with creatinine clearance. Total body clearance of mirtazapine was reduced approximately 30% in patients with moderate (Clcr = 11–39 mL/min/1.73 m²) and approximately 50% in patients with severe (Clcr = < 10 mL/min/1.73 m²) renal impairment when compared to normal subjects. Caution is indicated in administering REMERONSolTab® to patients with compromised renal function (see PRECAUTIONS and DOSAGE AND ADMINISTRATION).

Hepatic Insufficiency

Following a single 15 mg oral dose of REMERON®, the oral clearance of mirtazapine was decreased by approximately 30% in hepatically impaired patients compared to subjects with normal hepatic function. Caution is indicated in administering REMERONSolTab® to patients with compromised hepatic function (see PRECAUTIONS and DOSAGE AND ADMINISTRATION).

Clinical Trials Showing Effectiveness

The efficacy of REMERON® (mirtazapine) Tablets as a treatment for major depressive disorder was established in four placebo-controlled, 6-week trials in adult outpatients meeting DSM-III criteria for major depressive disorder. Patients were titrated with mirtazapine from a dose range of 5 mg up to 35 mg/day. Overall, these studies demonstrated mirtazapine to be superior to placebo on at least three of the following four measures: 21-Item Hamilton Depression Rating Scale (HDRS) total score; HDRS Depressed Mood Item; CGI Severity score; and Montgomery and Asberg Depression Rating Scale (MADRS). Superiority of mirtazapine over placebo was also found for certain factors of the HDRS, including anxiety/somatization factor and sleep disturbance factor. The mean mirtazapine dose for patients who completed these four studies ranged from 21–32 mg/day. A fifth study of similar design utilized a higher dose (up to 50 mg) per day and also showed effectiveness.

Continued on next page

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carin and atopic der[illegible]
n premedicant prior
ia premedication and p[illegible]
oxytrin may potentiate[illegible]
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should be modified on [illegible]
other barbiturates.
troxyzine is not known [illegible]
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o not use epinephrine, as Vistar
ine. Caffeine and Sodium Benz
e used to counteract central n
ffects.
ne antidote. It is doubtful that
any value in the treatment of
s. However, if other agents are

body fluids or tissue after its ingestion or ad-

[illegible] relief of anxiety and tension associated
[illegible]neurosis and as an adjunct in organic states
which anxiety is manifested in adults, 50–100 mg
[illegible]nted under 8 years, 50 mg daily in divided doses;
[illegible] years, 50–100 mg daily in divided doses.
[illegible] management of pruritus due to allergic con-
[illegible]s chronic urticaria and atopic and contact der-
[illegible] and its histamine-mediated pruritus: in adults,
[illegible] 50 mg daily; children under 6 years, 50 mg daily in
[illegible]ed and over 6 years, 50–100 mg daily in divided
[illegible]

[illegible]ere when used as a premedication and following
[illegible]sis: 50–100 mg in adults, and 0.6 mg/kg in

[illegible]reatment is initiated by the intramuscular route of
[illegible], subsequent dosage may be administered

[illegible] medications, the dosage should be adjusted ac-
[illegible] patient's response to therapy.

[illegible]PPLIED
[illegible]ules (hydroxyzine pamoate equivalent to
[illegible] hydrochloride)
[illegible] 100% (NDC 0069-5410-66), two-tone green
[illegible]
[illegible] 100% (NDC 0069-5420-66), green and white
[illegible]sules
[illegible] 100% (NDC 0069-5430-66), green and gray
[illegible]sules
[illegible] Oral Suspension (hydroxyzine pamoate equiva-
[illegible] 25 mg hydroxyzine hydrochloride per teaspoonful)
[illegible] pint (473 mL) bottles (NDC 0069-5440-93) and
[illegible] gallon bottles (NDC 0069-5440-97) in package

[illegible]rescently until product is completely resuspended.

[illegible]RAPHY
[illegible] as required.

[illegible]ed by:
[illegible] Lake
[illegible] Pfizer Inc, NY, NY 10017

Printed in U.S.A.
Revised Oct. 2001

[illegible]TARIL®
[illegible] hydrochloride
[illegible]MUSCULAR SOLUTION
Intramuscular Use Only

[illegible]

[illegible]-hydroxyethyl 4-[3-(p-fluorophenyl)-3-oxopropyl]-1-piperidineacetate dihydrochloride) is unrelated chemically to phenothiazine, reserpine, and meprobamate. Studies have demonstrated its clinical effectiveness in psychotherapeutic aspect of the total management of anxiety and emotional disturbances manifested by anxiety, tension, apprehension or confusion.

[illegible]ine has been shown clinically to be a rapid-acting [illegible]ic agent with a wide margin of safety. It induces a [illegible]ct of calmness, tension, psychosomatic adults and [illegible]n, without hypnotic children without impairing [illegible]ual alertness. It is not a cortical depressant, but its ac- [illegible]on may be due to suppression of activity in certain [illegible]s of the subcortical area of the central nervous sys-

[illegible]y skeletal muscle relaxation has been demonstrated [illegible]ntrarily.

[illegible]ine has been shown experimentally to have anti- [illegible] properties, apparently mediated through inter- [illegible]with the mechanism that responds to spasmogenic [illegible]ents such as serotonin, acetylcholine and histamine. [illegible]ble effects have been demonstrated experimen- [illegible]and clinically.

[illegible]netic effects, such as the opomorphine test and the [illegible]ool test, has been demonstrated. Pharmacological and [illegible]al studies indicate that hydroxyzine in therapeutic [illegible]ge does not increase gastric secretion or acidity and in [illegible] does provides mild antisecretory benefits.

[illegible]CATIONS

[illegible]ed management of anxiety, tension, and psychomotor [illegible]ce in conditions of emotional stress requires in most [illegible]s, a combined approach of psychotherapy and [illegible]therapy. Hydroxyzine has been found to be particu- [illegible]rly useful for this latter phase of therapy in its ability to [illegible] the disturbed patient more amenable to psychother- [illegible]. Long term treatment of the psychoneurotic and psy- [illegible]s although it should not be used as the sole treatment [illegible]s or of clearly demonstrated cases of depression. [illegible]ine is also useful in alleviating the manifestations [illegible]ty and tension as in the preparation for dental pro- [illegible]ed in acute emotional problems. It has also been [illegible]ended for the management of anxiety associated

[illegible]ity, such as in asthma, chronic urticaria, and pruritus.
VISTARIL (hydroxyzine hydrochloride) Intramuscular Solution is useful in treating the following types of patients when intramuscular administration is indicated:
1. The acutely disturbed or hysterical patient.
2. The acute or chronic alcoholic with anxiety withdrawal symptoms or delirium tremens.
3. As pre- and postoperative and pre- and postpartum adjunctive medication to permit reduction in narcotic dosage, allay anxiety and control emesis.

VISTARIL (hydroxyzine hydrochloride) has also demonstrated effectiveness in controlling nausea and vomiting, excluding motion and vomiting of pregnancy. (See Contraindications.)

In preoperative states, the reduction in narcotic requirement effected by hydroxyzine is of particular benefit to both mother and neonate.

Hydroxyzine benefits the cardiac patient by its ability to allay the associated anxiety and apprehension attendant to certain types of heart disease. Hydroxyzine is not known to interfere with the cardiac rhythm in any way and may be used concurrently with this agent.

The effectiveness of hydroxyzine in long term use, that is, more than 4 months, has not been evaluated in controlled clinical studies. The physician should reassess periodically the usefulness of the drug for the individual patient.

CONTRAINDICATIONS

Hydroxyzine hydrochloride intramuscular solution is intended only for intramuscular administration and should not, under any circumstances, be injected subcutaneously, into arterial, or intravenous sites.

This drug is contraindicated for patients who have shown a previous hypersensitivity to it.

Hydroxyzine, when administered to the pregnant mouse, rat, and rabbit, induced fetal abnormalities in the rat at doses substantially above the human therapeutic range. Clinical data in human beings are inadequate to establish safety in early pregnancy. Until such data are available, hydroxyzine is contraindicated in early pregnancy.

PRECAUTIONS

THE POTENTIATING ACTION OF HYDROXYZINE MUST BE CONSIDERED WHEN THE DRUG IS USED IN CONJUNCTION WITH CENTRAL NERVOUS SYSTEM DEPRESSANTS SUCH AS NARCOTICS, BARBITURATES, AND ALCOHOL. Rarely, cardiac arrests and death have been reported in association with the combined use of hydroxyzine hydrochloride IM and other CNS depressants. Therefore when central nervous system depressants are administered concomitantly with hydroxyzine their dosage should be reduced up to 50 per cent. The efficacy of hydroxyzine as adjunctive pre- and postoperative sedative medication has also been well established, especially as regards its ability to allay anxiety, control emesis, and reduce the amount of narcotic required.

HYDROXYZINE MAY POTENTIATE NARCOTICS AND BARBITURATES, so their use in premedicative adjunctive therapy should be modified as an individual basis. Atropine and other belladonna alkaloids are not affected by the drug.

When hydroxyzine is used preoperatively or prepartum, narcotic requirements may be reduced as much as 50 per cent. Thus, when 50 mg of VISTARIL (hydroxyzine hydrochloride) Intramuscular Solution is employed, meperidine dosage may be reduced from 100 mg to 50 mg. The administration of meperidine may result in severe hypotension in the postoperative patient or any individual whose ability to maintain blood pressure has been compromised by a depleted blood volume. Meperidine should be used with great caution and in reduced dosage in patients who are receiving other pre- and/or postoperative medications and in whom there is a risk of respiratory depression, hypotension, and prolonged sedation or unwarranted sedation. Since many medications concomitant with hydroxyzine, the manufacturer's prescribing information should be read carefully.

Since drowsiness may occur with the use of this drug, patients should be warned of this possibility and cautioned against driving a car or operating dangerous machinery while taking this drug.

As with all intramuscular preparations, VISTARIL Intramuscular Solution should be injected well within the body of a relatively large muscle. Inadvertent subcutaneous injection may result in significant tissue damage.

ADULTS: The preferred site is the upper outer quadrant of the buttock, (i.e., gluteus maximus), or the mid-lateral thigh.

CHILDREN: It is recommended that intramuscular injections be given preferably in the mid-lateral muscles of the thigh. In infants and small children the periphery of the upper outer quadrant of the gluteus muscle should be used only when necessary, such as in burn patients, in order to minimize the possibility of damage to the sciatic nerve.

The deltoid area should be used only if well developed such as in certain adults and older children, and then only with caution to avoid radial nerve injury. Intramuscular injections should not be made into the lower and mid-third of the upper arm. As with all intramuscular injections, aspiration is necessary to help avoid inadvertent injection into a blood vessel.

Geriatric Use: A determination has not been made whether controlled clinical studies of VISTARIL included sufficient numbers of subjects aged 65 and over to define a

responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal or cardiac function, and of concomitant disease or other drug therapy.

The extent of renal excretion of VISTARIL has not been determined. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selections.

Sedating drugs may cause confusion and over sedation in the elderly; elderly patients generally should be started on low doses of VISTARIL and observed closely.

ADVERSE REACTIONS

Therapeutic doses of hydroxyzine seldom produce impairment of mental alertness. However, drowsiness may occur; if so, it is usually transitory and may disappear in a few days of continued therapy or upon reduction of the dose. Dryness of the mouth may be encountered at higher doses. Extensive clinical use has substantiated the absence of toxic effects on the liver or bone marrow when administered in the recommended dosage for as long as four years of uninterrupted therapy. The absence of adverse effects has been further demonstrated in experimental studies in which excessively high doses were administered.

Involuntary motor activity, including rare instances of tremor and convulsions, has been reported, usually with doses considerably higher than those recommended. Continuous therapy with over one gram per day has been employed in some patients without these effects having been encountered.

DOSAGE AND ADMINISTRATION

The recommended dosage for VISTARIL (hydroxyzine hydrochloride) Intramuscular Solution are:

For adult psychiatric and emotional emergencies, including acute alcoholism.	IM: 50–100 mg stat, and q. 4–6h., p.r.o.
Nausea and vomiting excluding nausea and vomiting of pregnancy.	Adults: 25–100 mg IM
Pre- and postoperative adjunctive medication.	Children: 0.6 mg/lb body weight IM
Pre- and postpartum adjunctive therapy.	Adults: 25–100 mg IM Children: 0.6 mg/lb body weight IM 25–100 mg IM

As with all potent medications, the dosage should be adjusted according to the patient's response to therapy.

FOR ADDITIONAL INFORMATION OF THE ADMINISTRATION AND SITE OF SELECTION SEE PRECAUTIONS SECTION. NOTE: VISTARIL (hydroxyzine hydrochloride) Intramuscular Solution may be administered without further dilution.

Patients may be started on intramuscular therapy when indicated. They should be maintained on oral therapy whenever this route is practicable.

HOW SUPPLIED

VISTARIL (hydroxyzine hydrochloride) Intramuscular Solution.

Multi-Dose Vials

50 mg/mL: 10 mL vials (NDC 0049-5460-74)

STORAGE

Store below 86°F (30°C). Protect from freezing.

Distributed by:
Pfizer Roerig
Division of Pfizer Inc, NY, NY 10017

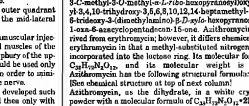
Printed in U.S.A.
Revised Oct. 2001

70-0843-00-6

ZITHROMAX®
(azithromycin tablets)
and
(azithromycin for oral suspension)

DESCRIPTION

ZITHROMAX® (azithromycin tablets and azithromycin for oral suspension) contain the active ingredient azithromycin, an azalide, a subclass of macrolide antibiotics, for oral administration. Azithromycin has the chemical name *(2R,3S,4R,5R,8R,10R,11R,12S,13S,14R)*- 13-[(2,6-dideoxy-3-*C*-methyl-3-*O*-methyl-α-*L*-*ribo*-hexopyranosyl)oxy]-2-ethyl-3,4,10-trihydroxy-3,5,6,8,10,12,14-heptamethyl-11-[[3,4,6-trideoxy-3-(dimethylamino)-β-*D*-*xylo*-hexopyranosyl]oxy]-1-oxa-6-azacyclopentadecan-15-one. Azithromycin is derived from erythromycin; however, it differs chemically from erythromycin in that a methyl-substituted nitrogen atom is incorporated into the lactone ring. Its molecular formula is $C_{38}H_{72}N_2O_{12}$, and its molecular weight is 749.00. Azithromycin has the following structural formula:



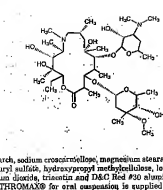
Each tablet contains azithromycin dihydrate equivalent to 250 mg or 500 mg azithromycin and the following inactive ingredients: dibasic calcium phosphate anhydrous, pregelatinized

Continued on next page

Consult 2004 PDR supplements and future editions for revisions

Serum $AUC_{0-\infty}$ (µg•hr/mL)		17.4 (6.2)*	14.9 (2.1)*
Serum $T_{\frac{1}{2}}$		71.8 hr	68.9 hr

*Total AUC for the entire 3-day and 5-day regimens



starch, sodium croscarmellose, magnesium stearate, sodium lauryl sulfate, hydroxypropyl methylcellulose, lactose, titanium dioxide, triacetin, and D&C Red #30 aluminum lake. ZITHROMAX® for oral suspension is supplied as bottles containing azithromycin dihydrate powder equivalent to 300 mg, 600 mg, 900 mg, or 1200 mg azithromycin per bottle and the following inactive ingredients: sucrose; sodium phosphate, tribasic, anhydrous; hydroxypropyl cellulose; xanthan gum; FD&C Red #40; and spray dried artificial cherry, creme de vanilla and bannana flavors. After constitution, each 5 mL of suspension contains 100 mg or 200 mg of azithromycin.

CLINICAL PHARMACOLOGY

Pharmacokinetics

Following oral administration of a single 500 mg dose (two 250 mg tablets) to 36 fasted healthy male volunteers, the mean (SD) pharmacokinetic parameters were AUC_{0-120} = 4.3 (1.2) µg•hr/mL; C_{max} = 0.5 (0.2) µg/mL; T_{max} = 2.5 (0.9) hours.

With a regimen of 500 mg (two 250 mg capsules*) on day 1, followed by 250 mg daily (one 250 mg capsule) on days 2 through 5, the pharmacokinetic parameters of azithromycin in plasma in healthy young adults (18-26 years of age) are portrayed in the chart below. C_{max} and C_{max} remained essentially unchanged from day 2 through day 5 of therapy.

Pharmacokinetic Parameters (Mean)	Total n=12 Day 1	Day 5
C_{max} (µg/mL)	0.41	0.24
T_{max} (h)	2.5	3.2
AUC_{0-24} (µg•hr/mL)	2.6	2.1
C_{24h} (µg/mL)	0.05	0.05
Urinary Excret. (% dose)	4.5	6.6

*Azithromycin 250 mg tablets are bioequivalent to 250 mg capsules in the fasted state. Azithromycin 250 mg capsules are no longer commercially available.

In a two-way crossover study, 12 adult healthy volunteers (6 males, 6 females) received 1,600 mg of azithromycin administered in single daily dosing either 5 days (two 250 mg tablets on day 1, followed by one 250 mg tablet on days 2-5) or 3 days (500 mg per day for days 1-3). Due to limited serum samples on day 2 (3-day regimen) and days 2-4 (5-day regimen), the serum concentration-time profile of each subject was fit to a 2-compartment model and the $AUC_{0-\infty}$ for the fitted concentration profile was comparable between the 5-day and 3-day regimens.

[See first table above]

Median azithromycin exposure (AUC_{0-24h}) in mononuclear (MN) and polymorphonuclear (PMN) leukocytes following either the 3- or 5-day regimens were more than a 100- to 800-fold greater than in serum, respectively. Administration of the same total dose with either the 5-day or 3-day regimen may be expected to provide comparable concentrations of azithromycin within MN and PMN leukocytes.

Two azithromycin 250 mg tablets are bioequivalent to a single 500 mg tablet.

Absorption

The absolute bioavailability of azithromycin 250 mg capsules is 38%.

In a two-way crossover study in which 12 healthy subjects received a single 500 mg dose of azithromycin (two 250 mg tablets) with or without a high fat meal, food was shown to increase C_{max} by 23% but had no effect on AUC.

When azithromycin suspension was administered with food to 28 adult healthy male subjects, C_{max} increased by 56% and AUC was unchanged.

The AUC of azithromycin was unaffected by co-administration of an antacid containing aluminum and magnesium hydroxide with azithromycin capsules; however, the C_{max} was reduced by 24%. Administration of cimetidine (800 mg) two hours prior to azithromycin had no effect on azithromycin absorption.

Distribution

The serum protein binding of azithromycin is variable in the concentration range approximating human exposure, decreasing from 51% at 0.02 µg/mL to 7% at 1 µg/mL.

Following oral administration, azithromycin is widely distributed throughout the body with an apparent steady-state volume of distribution of 31.1 L/kg. Greater azithromycin concentrations in tissues than in plasma or serum were observed. High tissue concentrations should not be interpreted to be quantitatively related to clinical efficacy. The antimicrobial activity of azithromycin is pH related and appears to be reduced with decreasing pH. However, the extensive distribution of drug to tissues may be relevant to clinical activity.

Selected tissue (or fluid) concentration and tissue (or fluid) to plasma/serum concentration ratios are shown in the following table:

[See second table above]

The extensive tissue distribution was confirmed by examination of additional tissues and fluids (bone, ejaculum, prostate, ovary, uterus, adipose, stomach, liver, and gallbladder). As there are no data from adequate and well-controlled studies of azithromycin treatment of infections in these additional body sites, the clinical importance of these tissue concentration data is unknown.

Following a regimen of 500 mg on the first day and 250 mg daily for 4 days, only very low concentrations were noted in cerebrospinal fluid (less than 0.01 µg/mL) in the presence of non-inflamed meninges.

Metabolism

In vitro and *in vivo* studies to assess the metabolism of azithromycin have not been performed.

Elimination

Plasma concentrations of azithromycin following single 500 mg oral and i.v. dose declined in a polyexponential pattern with a mean apparent plasma clearance of 630 mL/min and terminal elimination half-life of 68 hours. The prolonged terminal half-life is thought to be due to extensive uptake and subsequent release of drug from tissues.

Biliary excretion of azithromycin, predominantly as unchanged drug, is a major route of elimination. Over the course of a week, approximately 6% of the administered dose appears as unchanged drug in urine.

Special Populations

Renal Insufficiency

Azithromycin pharmacokinetics were investigated in 42 adults (21 to 85 years of age) with varying degrees of renal impairment. Following the oral administration of a single 1,000 mg dose of azithromycin, mean C_{max} and AUC_{0-72} increased by 61% and 4.2%, respectively in subjects with mild to moderate renal impairment (GFR 10 to 80 mL/min) compared to subjects with normal renal function (GFR >80 mL/min). The mean C_{max} and AUC_{0-72} increased 61% and 35%, respectively in subjects with severe renal impairment (GFR <10 mL/min) compared to subjects with normal renal function (GFR >80 mL/min). (See DOSAGE AND ADMINISTRATION.)

Hepatic Insufficiency

The pharmacokinetics of azithromycin in subjects with hepatic impairment have not been established.

Gender

There are no significant differences in the disposition of azithromycin between male and female subjects. No dosage adjustment is recommended based on gender.

Geriatric Patients

When studied in healthy elderly subjects aged 65 to 85 years, the pharmacokinetic parameters of azithromycin in elderly men were similar to those in young adults; however, in elderly women, although higher peak concentrations (increased by 30 to 50%) were observed, no significant accumulation occurred.

Pediatric Patients

In two clinical studies, azithromycin for oral suspension was dosed at 10 mg/kg on day 1, followed by 5 mg/kg on days 2 through 5 to two groups of children (aged 1-5 years and 5-15 years, respectively). The mean pharmacokinetic parameters on day 5 were C_{max}=0.216 µg/mL, T_{max}=1.9 hours, AUC_{0-24}=1.822 µg•hr/mL for the 1- to 5-year-old group and were C_{max}=0.383 µg/mL, T_{max}=2.4 hours, AUC_{0-24}=3.109 µg•hr/mL for the 5- to 15-year-old group. Two clinical studies were conducted in 68 children aged 6 months to 5 years to determine the pharmacokinetics and safety of azithromycin for oral suspension in children. Azithromycin was administered following a low-fat breakfast.

The first study consisted of 35 pediatric patients treated with 30 mg/kg/day (maximum daily dose 500 mg) for 3 days, of whom 34 patients were evaluated for pharmacokinetics. In the second study, 33 pediatric patients received doses of 12 mg/kg/day (maximum daily dose 500 mg) for 5 days, of whom 31 patients were evaluated for pharmacokinetics. In both studies, azithromycin concentrations were determined over a 24 hour period following the last daily dose. Patients weighing above 25.0 kg in the 3-day study received 41.7 kg in the 5-day study received the maximum adult daily dose of 500 mg. Eleven patients (weighing 25.0 kg or less) in the first study and 17 patients (weighing 41.7 kg or less) in the second study received a total dose of 60 mg/kg. The following table shows pharmacokinetic data in the full set of children who received a total dose of 60 mg/kg:

Pharmacokinetic Parameters (mean [SD])	3-Day Regimen (20 mg/kg × 3 days)	5-Day Regimen (12 mg/kg × 5 days)
n	11	17
C_{max} (µg/mL)	1.1 (0.4)	0.5 (0.4)
T_{max} (hr)	2.7 (1.9)	2.2 (0.8)
AUC_{0-24} (µg•hr/mL)	7.9 (2.9)	3.9 (1.9)

The similarity of the overall exposure ($AUC_{0-\infty}$) between the 3-day and 5-day regimens in pediatric patients is unknown. Single dose pharmacokinetics in children given dose of 30 mg/kg have not been studied. (See DOSAGE AND ADMINISTRATION.)

Drug-Drug Interactions

Drug interaction studies were performed with azithromycin and other drugs likely to be co-administered. The effects of co-administration of azithromycin on the pharmacokinetics of other drugs are shown in Table 1 and the effect of other drugs on the pharmacokinetics of azithromycin are shown in Table 2.

Co-administration of azithromycin at therapeutic dose had a modest effect on the pharmacokinetics of the drugs listed in Table 1. No dosage adjustment of drugs listed in Table 1 is recommended when co-administered with azithromycin.

Co-administration of azithromycin with efavirenz or fluconazole had a modest effect on the pharmacokinetics of azithromycin. Neither significantly increased the C_{max} and AUC of azithromycin. No dosage adjustment of azithromycin is recommended when administered with drugs listed in Table 2. (See PRECAUTIONS - Drug interactions.)

[See table 1 at bottom of next page]

[See table 2 at top of page 2676]

Microbiology: Azithromycin acts by binding to the 50S ribosomal subunit of susceptible microorganisms and, thus, interfering with microbial protein synthesis. Nucleic acid synthesis is not affected.

Azithromycin concentrates in phagocytes and fibroblasts as demonstrated by *in vitro* incubation techniques. Using such methodology, the ratio of intracellular to extracellular concentration was >30 after one hour incubation. *In vivo* studies suggest that concentration in phagocytes may contribute to drug distribution to inflamed tissues.

AZITHROMYCIN CONCENTRATIONS FOLLOWING A 500 mg DOSE (TWO 250 mg CAPSULES) IN ADULTS

TISSUE OR FLUID	TIME AFTER DOSE (h)	TISSUE OR FLUID CONCENTRATION (µg/g or µg/mL)	CORRESPONDING PLASMA OR SERUM LEVEL (µg/mL)	TISSUE OR FLUID/PLASMA/SERUM RATIO
SKIN	72-96	0.4	0.012	35
LUNG	72-96	4.0	0.012	>100
SPUTUM*	2-4	1.0	0.64	2
SPUTUM**	10-12	2.9	0.1	30
TONSIL***	9-18	4.5	0.03	>100
TONSIL***	180	0.9	0.006	>100
CERVIX****	19	2.8	0.04	70

[1] Azithromycin tissue concentrations were originally determined using 250 mg capsules.

* Sample was obtained 2-4 hours after the first dose.

** Sample was obtained 10-12 hours after the first dose.

*** Dosing regimen of two doses of 250 mg each, separated by 12 hours.

**** Sample was obtained 19 hours after a single 500 mg dose.

Evidence of Infection	Total	Cure	Improved	Cure + Improved
Mycoplasma pneumoniae	18	11 (61%)	5 (28%)	16 (89%)
Chlamydia pneumoniae	34	15 (44%)	13 (38%)	28 (82%)
Legionella pneumophila	16	5 (31%)	8 (50%)	13 (81%)

ANIMAL TOXICOLOGY

Phospholipidosis (intracellular phospholipid accumulation) has been observed in some tissues of mice, rats, and dogs given multiple doses of azithromycin. It has been demonstrated in numerous organ systems (e.g., eye, dorsal root ganglia, liver, gallbladder, kidney, spleen, and pancreas) in dogs treated with azithromycin at doses which, expressed on a mg/kg basis, are only 2 times greater than the recommended adult human dose and in rats at doses comparable to the recommended adult human dose. This effect has been reversible after cessation of azithromycin treatment. Phospholipidosis has been observed to a similar extent in the tissues of neonatal rats and dogs given daily doses of azithromycin ranging from 10 days to 36 days. Based on the pharmacokinetic data, phospholipidosis has been seen in the rat (80 mg/kg dose) at observed C_{max} value of 1.3 µg/mL (6 times greater than the observed C_{max} of 0.216 µg/mL at the pediatric dose of 10 mg/kg). Similarly, it has been shown in the dog (10 mg/kg dose) at observed C_{max} value of 1.5 µg/mL (7 times greater than the observed same C_{max} and drug dose in the studied pediatric population). On mg/m² basis, 30 mg/kg dose in the rat (136 mg/m²) and 10 mg/kg dose in the dog (70 mg/m²) are approximately 0.4 and 0.6 times, respectively, the recommended dose in the pediatric patients with an average body weight of 25 kg. This effect, similar to that seen in the adult animals, is reversible after cessation of azithromycin treatment. The significance of these findings for animals and for humans is unknown.

REFERENCES

1. National Committee for Clinical Laboratory Standards. Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria that Grow Aerobically - Third Edition. Approved Standard NCCLS Document M7-A3, Vol. 13, No. 25, NCCLS, Villanova, PA, December, 1993.
2. National Committee for Clinical Laboratory Standards. Performance Standards for Antimicrobial Disk Susceptibility Tests - Fifth Edition. Approved Standard NCCLS Document M2-A5, Vol. 13, No. 24, NCCLS, Villanova, PA, December, 1993.

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NY, NY 10017
70-5191-00-7 Revised October 2002

Shown in Product Identification Guide, page 332

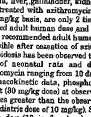
ZOLOFT®

(sertraline hydrochloride)

Tablets and Oral Concentrate

DESCRIPTION

ZOLOFT® (sertraline hydrochloride) is a selective serotonin reuptake inhibitor (SSRI) for oral administration. It has a molecular weight of 342.7. Sertraline hydrochloride has the following chemical name: (1*S*-*cis*)-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-*N*-methyl-1-naphthalenamine hydrochloride. The empirical formula $C_{17}H_{17}NCl_2 \cdot HCl$ is represented by the following structural formula:



Sertraline hydrochloride is a white crystalline powder that is slightly soluble in water and isopropyl alcohol, and sparingly soluble in ethanol.

ZOLOFT is supplied for oral administration as scored tablets containing sertraline hydrochloride equivalent to 25, 50 and 100 mg of sertraline and the following inactive ingredients: dibasic calcium phosphate dihydrate, *D & C* Yellow #10 aluminum lake (in 25 mg tablet), *FD & C* Blue #1 aluminum lake (in 25 mg tablet), *FD & C* Red #40 aluminum lake (in 25 mg tablet), *FD & C* Blue #2 aluminum lake

Information will be superseded by supplements and subsequent editions

titanium dioxide.

ZOLOFT oral concentrate is available in a multidose 60 mL bottle. Each mL of solution contains sertraline hydrochloride equivalent to 20 mg of sertraline. The solution contains the following inactive ingredients: glycerin, alcohol (12%), menthol, butylated hydroxytoluene (BHT). The oral concentrate must be diluted prior to administration (see PRECAUTIONS, Information for Patients and DOSAGE AND ADMINISTRATION).

CLINICAL PHARMACOLOGY

Pharmacodynamics

The mechanism of action of sertraline is presumed to be linked to its inhibition of CNS neuronal uptake of serotonin (5HT). Studies of clinically relevant doses in man have demonstrated that sertraline is a potent inhibitor of serotonin into human platelets. *In vitro* studies in animals also suggest that sertraline is a potent and selective inhibitor of neuronal serotonin reuptake and has only very weak effects on norepinephrine and dopamine neuronal reuptake. *In vitro* studies have shown that sertraline has no significant affinity for adrenergic (alpha-, beta-, alpha$_2$-, beta$_2$-), cholinergic, GABA, dopaminergic, histaminergic, serotonergic ($5HT_{1A}$, $5HT_{2A}$), or benzodiazepine receptors; antagonism of such receptors has been hypothesized to be associated with various anticholinergic, sedative, and cardiovascular effects for other psychotropic drugs. The chronic administration of sertraline was found in animals to downregulate brain norepinephrine receptors. This has been observed with other drugs effective in the treatment of major depressive disorder. Sertraline does not inhibit monoamine oxidase.

Pharmacokinetics

Systemic Bioavailability—In man, following oral once-daily dosing over the range of 50 to 200 mg for 14 days, mean peak plasma concentrations (Cmax) of sertraline occurred between 4.5 to 8.4 hours post-dosing. The average terminal elimination half-life of plasma sertraline is about 26 hours. Based on this pharmacokinetic parameter, steady-state sertraline plasma levels should be achieved after approximately one week of once-daily dosing. Linear dose-proportional pharmacokinetics was demonstrated in a single dose study in which the Cmax and area under the plasma concentration time curve (AUC) of sertraline were proportional to dose over a range of 50 mg to 150 mg. Consistent with the terminal elimination half-life, there is an approximately two-fold accumulation, compared to a single dose, of sertraline with repeated dosing over a 50 to 200 mg dose range. The single dose bioavailability of sertraline tablets is approximately equal to an equivalent dose of solution.

In a relative bioavailability study comparing the pharmacokinetics of 100 mg sertraline as an oral solution to a 100 mg sertraline tablet in 16 healthy adults, the solution to tablet ratio of geometric means AUC and Cmax values were 114.8% and 120.8%, respectively. 90% confidence intervals (CI) were within the range of 80–125% with the exception of the upper 90% CI for Cmax which was 126.0%.

The effects of food on the bioavailability of the sertraline tablet and oral concentrate were studied in subjects administered a single dose with and without food. For the tablet, AUC was slightly increased when drug was administered with food but the Cmax was 25% greater, while the time to reach peak plasma concentration (Tmax) decreased from 8 hours post-dosing to 5.5 hours. For the oral concentrate, Tmax was slightly prolonged from 6.9 hours to 7.0 hours with food.

Metabolism—Sertraline undergoes extensive first pass metabolism. The principal route of metabolism for sertraline is N-demethylation. N-demethylsertraline has a plasma terminal elimination half-life of 62 to 104 hours. Data in *vitro* hexadecandrane dye plasma protein binding have shown N-desmethylsertraline to be substantially less active than sertraline. Both sertraline and N-desmethylsertraline undergo oxidative deamination and subsequent reduction, hydroxylation, and glucuronide conjugation. In a study of radiolabeled sertraline involving two healthy male subjects, sertraline accounted for less than 5% of the plasma radioactivity. About 40-45% of the administered radioactivity was recovered in urine in 9 days. Unchanged sertraline was not detectable in the urine. For the same period, about 40-45% of the administered radioactivity was accounted for in feces, including 12-14% unchanged sertraline.

Desmethylsertraline exhibits time-related, dose dependent increases in AUC (0-24 hour), Cmax and Cmin, with about a 2-9 fold increase in these pharmacokinetic parameters between day 1 and day 14.

Protein Binding—*In vitro* protein binding studies performed with radiolabeled 3H-sertraline showed that sertraline is highly bound to serum proteins (98%) in the range of 20 to 500 ng/mL. However, at up to 300 and 200 ng/mL concentrations, respectively, sertraline and N-desmethylsertraline did not alter the plasma protein binding of two other highly protein bound drugs, viz., warfarin and propranolol (see PRECAUTIONS).

Pediatric Pharmacokinetics—Sertraline pharmacokinetics were evaluated in a group of 61 pediatric patients (29 aged 6-12 years, 32 aged 13-17 years) with a DSM-III-R diagnosis of major depressive disorder or obsessive-compulsive disorder. On the basis of weight, the 6-12 year old group received sertraline 200 mg/day, the 6-12 year old group received sertraline AUC (0-24 hr) of 3107 ng·hr/mL, Cmax of 165 ng/mL, and mean half-life of 25.3 hr. The 13-17 year old group exhibited a mean sertraline AUC (0-24 hr) of 2296 ng·hr/mL, mean Cmax of 137 ng/mL, and mean half-life of 27.8 hr. Higher plasma levels in the 6-12 year group were largely attributable to patients with lower body weights. No gender related differences were observed. By comparison, a group of 22 supportively studied adults between 18 and 45 years of age (11 male, 11 female) given 50 days of 200 mg/day sertraline and exhibited a mean sertraline AUC (0-24 hr) of 2570 ng·hr/mL, mean Cmax of 142 ng/mL, and mean half-life of 27.2 hr. Relative to adults, both the 6-12 year olds and the 13-17 year olds showed about 22% lower AUC (0-24 hr). Cmax values when plasma concentration was adjusted for weight. These data suggest that pediatric patients metabolize sertraline with slightly greater efficiency than adults. Nevertheless, lower doses may be advisable for pediatric patients with their lower body weights, especially in very young patients in order to avoid excessive plasma levels (see DOSAGE AND ADMINISTRATION).

Age—Sertraline plasma clearance in a group of 16 (8 male, 8 female) elderly patients treated for 14 days at a dose of 100 mg/day was approximately 40% lower than in a similarly studied group of younger (25 to 32 y.o.) individuals (see DOSAGE AND ADMINISTRATION). Steady-state should be achieved after 2 to 3 weeks in older patients. The mean steady-state AUC increased clearance of desmethylsertraline in older males, but not in older females.

Liver Disease—As might be predicted from its primary site of metabolism, liver impairment can affect the elimination of sertraline. In a study of volunteers with mild liver impairment (N=10, 5 patients with Child-Pugh scores of 5-6 and 5 patients with Child-Pugh scores of 7-8) who received 50 mg sertraline per day for 10 days, the AUC and half-life of sertraline were increased, resulting in approximately 3-fold greater exposure compared to age-matched volunteers with no hepatic impairment (N=10). The exposure to desmethylsertraline was approximately 2-fold greater compared to age-matched volunteers with no hepatic impairment. There were no significant differences in protein binding observed between the two groups. The effects of sertraline in patients with moderate or severe hepatic impairment have not been studied. The results suggest that the use of sertraline in patients with liver disease must be approached with caution. If the decision is made to administer sertraline to liver impairment, a lower or less frequent dose should be used (see PRECAUTIONS and DOSAGE AND ADMINISTRATION).

Renal Disease—Sertraline is extensively metabolized and excretion of unchanged drug in urine is a minor route of elimination. In volunteers with mild to moderate (CLcr=35-65 mL/min), moderate to severe (CLcr=10-29 mL/min) or severe (requiring hemodialysis) renal impairment (N=10 each group), the pharmacokinetic and protein binding of 200 mg sertraline per day maintained for 21 days were not altered compared to age-matched volunteers with no renal impairment. Thus sertraline multiple dose pharmacokinetics appear to be unaffected by renal impairment (see PRECAUTIONS).

Clinical Trials

Major Depressive Disorder—The efficacy of ZOLOFT as a treatment for major depressive disorder was established in two placebo-controlled studies in adult outpatients meeting DSM-III criteria for major depressive disorder. Study 1 was an 8-week study with flexible dosing of ZOLOFT in a range of 50 to 200 mg/day; the mean dose for completers was 146 mg/day. Study 2 was a 6-week fixed-dose study including ZOLOFT doses of 50, 100, and 200 mg/day. Overall, these studies demonstrated ZOLOFT to be superior to placebo on the Hamilton Depression Rating Scale and the Clinical Global Impression Severity and Improvement scales. Study 2 was not readily interpretable regarding a dose response relationship for effectiveness.

Study 3 involved depressed outpatients who had responded to the end of an initial 8-week open treatment phase on ZOLOFT 50-200 mg/day. Those patients (N=295) were randomized to continuation for 44 weeks on double-blind ZOLOFT 50-200 mg/day or placebo. A statistically significantly lower relapse rate was observed for patients taking ZOLOFT compared to those on placebo. The mean dose for completers was 70 mg/day.

Analyses for gender effects on outcome did not suggest any differential responsiveness on the basis of sex.

Obsessive-Compulsive Disorder (OCD)—The effectiveness of ZOLOFT in the treatment of OCD was demonstrated in three multicenter placebo controlled studies of adult outpatients (Studies 1-3). Patients in all studies had moderate to severe OCD (DSM-III or DSM-III-R) with mean baseline ratings on the Yale-Brown Obsessive-Compulsive Scale (YBOCS) total score ranging from 23 to 25.

Study 1 was an 8-week study with flexible dosing of ZOLOFT in a range of 50 to 200 mg/day; the mean dose for completers was 186 mg/day. Patients receiving ZOLOFT experienced a mean reduction of approximately 4 points on the YBOCS total score which was significantly greater than the mean reduction of 2 points in placebo treated patients

The safety and efficacy of WelChol® in patients with dysphagia, swallowing disorders, severe gastrointestinal motility disorders, or major gastrointestinal tract surgery have not been established. Consequently, caution should be exercised when WelChol® is used in patients with these gastrointestinal disorders.

Information for the Patient

WelChol® may be taken once per day with a meal, or taken twice per day in divided doses with meals. Patients should be directed to take WelChol® with a liquid and a meal, and either to their NCEP-recommended diet. Patients should tell their physicians if they are pregnant, are intending to become pregnant, or are breastfeeding.

Laboratory Tests

Serum total-C, LDL-C and TG levels should be determined periodically based on NCEP guidelines to confirm favorable initial and adequate long-term responses.

Drug Interactions

WelChol® has been studied in several human drug interaction studies in which it was administered with a meal and the test drug. WelChol® was found to have no significant effect on the bioavailability of digoxin, lovastatin, metoprolol, quinidine, valproic acid, and warfarin. WelChol® decreased the C_{max} and AUC of sustained-release verapamil (Calan SR®) by approximately 31% and 11%, respectively. Since there is a high degree of variability in the bioavailability of verapamil, the clinical significance of this finding is unclear. In clinical studies, co-administration of WelChol® with atorvastatin, lovastatin, or simvastatin did not interfere with the lipid-lowering activity of the HMG-CoA reductase inhibitor. Other drugs have not been studied. When administering other drugs for which alterations in blood levels could have a clinically significant effect on safety or efficacy, physicians should consider monitoring drug levels or effects.

Carcinogenesis, Mutagenesis, Impairment of Fertility

A 104-week carcinogenicity study with colesevelam (WelChol®) was conducted in CD-1 mice, at oral dietary doses up to 3 g/kg/day. This dose was approximately 50 times the maximum recommended human dose of 4.5 g/day, based on body weight, mg/kg. There were no significant drug-induced tumor findings in male or female mice. In a 104-week carcinogenicity study with colesevelam (WelChol®) in Harlan Sprague-Dawley rats, a statistically significant increase in the incidence of pancreatic acinar cell adenoma was seen in male rats at doses >1.2 g/kg/day (approximately 20 times the maximum human dose, based on body weight, mg/kg) (tested test only). A statistically significant increase in thyroid C-cell adenoma was seen in female rats at 2.4 g/kg/day (approximately 40 times the maximum human dose, based on body weight, mg/kg).

Colesevelam and four degradants present in the drug substance have been evaluated for mutagenicity in the Ames test and a mammalian chromosomal aberration test. The four degradants and an extract of the parent compound did not exhibit genetic toxicity in an *in vitro* bacterial mutagenesis assay (in *S. typhimurium* and *E. coli* (Ames assay) with or without rat liver metabolic activation. An extract of the parent compound was positive in the Chinese Hamster Ovary (CHO) cell chromosomal aberration assay in the presence of metabolic activation and negative in the absence of metabolic activation. The results of the CHO cell chromosomal aberration assay with two of the four degradants, decylamine HCl and aminohexyltrimethyl ammonium chloride HCl, were equivocal in the absence of metabolic activation and negative in the presence of metabolic activation. The other two degradants, didecylamine HCl and 6-decylamino-hexyltrimethyl ammonium chloride HCl, were negative in the presence and absence of metabolic activation.

Colesevelam did not impair fertility in rats at doses of up to 3 g/kg/day (approximately 50 times the maximum human dose, based on body weight, mg/kg).

PREGNANCY

Pregnancy Category B

Reproduction studies have been performed in rats and rabbits at doses up to 3 g/kg/day and 1 g/kg/day, respectively (approximately 50 and 17 times the maximum human dose, based on body weight, mg/kg) and have revealed no evidence of harm to the fetus due to colesevelam. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed. Requirements for vitamins and other nutrients are increased in pregnancy. The effect of WelChol® on the absorption of vitamins has not been studied in pregnant women.

Pediatric Use

The safety and efficacy of colesevelam (WelChol®) have not been established in pediatric patients.

Geriatric Use

There is no evidence for special considerations when colesevelam (WelChol®) is administered to elderly patients.

ADVERSE REACTIONS

WelChol® treatment-emergent adverse events that occurred in greater than 2% of patients in an integrated safety analysis are presented in Table 4.

RISK CATEGORY	LDL-C GOAL	TO INITIATE THERAPEUTIC LIFESTYLE CHANGES (TLC)	TO CONSIDER DRUG THERAPY
CHD or CHD Risk Equivalents (10-year risk >20%)	<100 mg/dL	≥100 mg/dL	≥130 mg/dL (100–129 mg/dL: drug optional)*
2+ Risk Factors (10-year risk ≤20%)	<130 mg/dL	≥130 mg/dL	10-year risk 10-20%: ≥130 mg/dL 10-year risk <10%: ≥160 mg/dL
0-1 Risk Factor†	<160 mg/dL	≥160 mg/dL	≥190 mg/dL (160–189 mg/dL: LDL-lowering drug optional)

*Some authorities recommended use of LDL cholesterol-lowering drugs in the category if LDL cholesterol <100 cannot be achieved by therapeutic lifestyle changes. Other prefer use of drugs that primarily modify triglycerides and HDL cholesterol e.g., nicotinic acid or fibrate. Clinical judgment also may call for deferring drug therapy in this subcategory.
†Almost all people with 0-1 risk factor have a 10-year risk <10%, thus 10-year risk assessment in people with 0-1 risk factor is not necessary.

Table 4: Frequent (≥2%) Treatment-Emergent Adverse Events By Treatment Category

BODY SYSTEM/ ADVERSE EVENT	PLACEBO (N=258) %	WELCHOL® ONLY (N=807) %
Body as a Whole		
Infection	13	10
Headache	8	6
Pain	7	5
Back Pain	6	3
Abdominal Pain	5	5
Flu Syndrome	3	3
Accidental Injury	3	4
Asthenia	2	4
Digestive System		
Flatulence	14	12
Constipation	7	11
Diarrhea	7	6
Nausea	4	4
Dyspepsia	3	8
Respiratory System		
Sinusitis	4	2
Rhinitis	3	3
Cough Increased	2	2
Pharyngitis	2	3
Musculoskeletal System		
Myalgia	0	2

OVERDOSAGE

Because WelChol® is not absorbed, the risk of systemic toxicity is low. Doses in excess of 4.8 g per day have not been tested.

DOSAGE AND ADMINISTRATION

Monotherapy

The recommended starting dose of WelChol® is 3 tablets taken twice per day with meals or 6 tablets once per day with a meal. The WelChol® dose can be increased to 7 tablets, depending upon the desired therapeutic effect. WelChol® should be taken with a liquid.

Combination Therapy

WelChol®, at doses of 4 to 6 tablets per day, has been shown to be safe and effective when dosed at the same time (i.e., co-administered) as an HMG-CoA reductase inhibitor or when the two drugs are dosed apart. (CLINICAL PHARMACOLOGY, Clinical Trials). WelChol® should be taken with a liquid. For maximal therapeutic effect in combination with an HMG-CoA reductase inhibitor, the recommended dose of WelChol® is 3 tablets taken twice per day with meals or 6 tablets taken once per day with a meal.

HOW SUPPLIED

WelChol® (colesevelam hydrochloride), 625 mg, is supplied as an off-white, solid tablet imprinted with the word "Sankyo" over "C01".

WelChol® Tablets are available as follows:
Bottles of 180—NDC 65597-701-18
Bottles of 24—NDC 65597-701-24
Storage
Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F)[see USP Controlled Room Temperature]. Protect from exposure to 40°C does not adversely affect the product. Protect from moisture.

References

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2. Shepherd J, Packard CJ, Bicker S, Velcht LTD, George MH. Cholestyramine promotes receptor-mediated low-density-lipoprotein catabolism. N Engl J Med 1980; 302: 1219-22.
3. Friedewald WT, Levy RI, Fredrickson DS: Estimation of the concentration of LDL cholesterol in plasma without use of a preparative ultracentrifuge. Clin. Chem. 1972; 18(6): 499.

Manufactured for: Sankyo Pharma Inc.
Parsippany, New Jersey 07054
by: Patheon YM Inc.
Toronto, Ontario M3B 1Y5
Active Ingredient: Product of Austria
Licensed From: GelTex Pharmaceuticals, Inc.
Issued: March 2003
Version: 6

Shown in Product Identification Guide, page 334

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(212) 551-4000

For Medical Information Contact:
Product Information Services
(800) 446-6207

Sales and Ordering:
East Coast: (800) 223-1062
West Coast: (800) 223-5511

DESCRIPTION

Ambien (zolpidem tartrate), is a non-benzodiazepine hypnotic of the imidazopyridine class and is available in 5-mg and 10-mg strength tablets for oral administration.
Chemically, zolpidem is N,N,6-trimethyl-2-p-tolylimidazo[1,2-a] pyridine-3-acetamide L-/+)-tartrate (2:1). It has the following structure:
[See chemical structure at top of next column]
Zolpidem tartrate is a white to off-white crystalline powder that is sparingly soluble in water, alcohol, and propylene glycol. It has a molecular weight of 764.88.
Each Ambien tablet includes the following inactive ingredients: hydroxypropyl methylcellulose, lactose, magnesium stearate, microcrystalline cellulose, polyethylene glycol,

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n Guide, page 334

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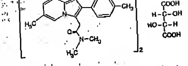


sodium starch glycolate, and titanium dioxide; the 5-mg tablet also contains FD&C Red No. 40, iron oxide colorant, and polysorbate 80.

CLINICAL PHARMACOLOGY

Pharmacodynamics: Subunit modulation of the $GABA_A$ receptor chloride channel macromolecular complex is hypothesized to be responsible for sedative, anticonvulsant, anxiolytic, and myorelaxant drug properties. The major modulatory site of the $GABA_A$ receptor complex is located on its alpha (α) subunit and is referred to as the benzodiazepine (BZ) or omega (ω) receptor. At least three subtypes of the (ω) receptor have been identified.

While zolpidem is a hypnotic agent with a chemical structure unrelated to benzodiazepines, barbiturates, or other drugs with known hypnotic properties, it interacts with a GABA-BZ receptor complex and shares some of the pharmacological properties of the benzodiazepines. In contrast to the benzodiazepines, which nonselectively bind to and activate all omega receptor subtypes, zolpidem in vitro binds the (ω_1) receptor preferentially with a high affinity ratio of the $alpha_1/alpha_5$ subunits. The (ω_1) receptor is found primarily on the Lamina IV of the sensorimotor cortical regions, substantia nigra (pars reticulata), cerebellum molecular layer, olfactory bulb, ventral thalamic complex, pons, inferior colliculus, and globus pallidus. This selective binding of zolpidem on the (ω_1) receptor is not absolute, but it may explain the relative absence of myorelaxant and anticonvulsant effects in animal studies as well as the preservation of deep sleep (stages 3 and 4) in human studies of zolpidem at hypnotic doses.

Pharmacokinetics: The pharmacokinetic profile of Ambien is characterized by rapid absorption from the GI tract and a short elimination half-life ($T_{1/2}$) in healthy subjects. In a single-dose crossover study in 45 healthy subjects administered 5- and 10-mg zolpidem tartrate tablets, the mean peak concentrations (C_{max}) were 59 (range: 29 to 113) and 121 (range: 58 to 272) ng/mL, respectively, occurring at a mean time (T_{max}) of 1.6 hours for both. The mean Ambien elimination half-life was 2.6 (range: 1.4 to 4.5) and 2.5 (range: 1.4 to 3.8) hours, for the 5- and 10-mg tablets, respectively. Ambien is converted to inactive metabolites that are eliminated primarily by renal excretion. Ambien demonstrated linear kinetics in the dose range of 5 to 20 mg. Total protein binding was found to be 92.5 ± 0.1% and remained constant, independent of concentration between 40 and 790 ng/mL. Zolpidem did not accumulate in young adults following nightly dosing with 20-mg zolpidem tartrate tablets for 2 weeks.

A food-effect study in 30 healthy male volunteers compared the pharmacokinetics of Ambien 10 mg when administered while fasting or 20 minutes after a meal. Results demonstrated that with food, mean AUC and C_{max} were decreased by 15% and 25%, respectively, while mean T_{max} was prolonged by 60% (from 1.4 to 2.2 hr). The half-life remained unchanged. These results suggest that, for faster sleep onset, Ambien should not be administered with or immediately after a meal.

In the elderly, the dose for Ambien should be 5 mg (see *Precautions and Dosage and Administration*). This recommendation is based on several studies in which the mean C_{max}, $T_{1/2}$, and AUC were significantly increased when compared to results in young adults. In one study of eight elderly subjects (>70 years), the means for C_{max}, $T_{1/2}$, and AUC significantly increased by 50% (255 vs 384 ng/mL), 32% (2.2 vs 2.9 hr), and 64% (955 vs 1,562 ng hr/mL), respectively, as compared to younger adults (20 to 40 years) following a single 20-mg oral zolpidem dose. Ambien did not accumulate in elderly subjects following nightly oral dosing of 10 mg for 1 week.

The pharmacokinetics of Ambien in eight patients with chronic hepatic insufficiency were compared to results in healthy subjects. Following a single 20-mg oral zolpidem dose, mean C_{max} and AUC were found to be two times (250 vs 499 ng/mL) and five times (788 vs 4,203 ng hr/mL) higher, respectively, in hepatically compromised patients. T_{max} did not change. The mean half-life in cirrhotic patients of 9.9 hr (range: 4.1 to 25.8 hr) was greater than that observed in normals of 2.2 hr (range: 1.6 to 2.4 hr). Dosing should be modified accordingly in patients with hepatic insufficiency (see *Precautions and Dosage and Administration*).

The pharmacokinetics of zolpidem tartrate were studied in 11 patients with end-stage renal failure (mean Cl_{Cr} = 6.5 ± 1.5 mL/min) undergoing hemodialysis three times a week, who were dosed with zolpidem 10 mg orally each day for 14 or 21 days. No statistically significant differences were observed for C_{max}, T_{max}, half-life, and AUC between the first and last day of drug administration when baseline concentration adjustments were made. On day 1, C_{max} was 172 ± 29 ng/mL (range: 46 to 344 ng/mL). After repeated dosing for 14 or 21 days, C_{max} was 203 ± 32 ng/mL (range: 28 to 316 ng/mL). On day 1, T_{max} was 1.7 ± 0.3 hr (range: 0.5 to 3.0 hr); after repeated dosing T_{max} was 0.8 ± 0.2 hr (range: 0.5 to 2.0 hr). This variation is accounted for by noting that last-day serum sampling began 10 hours after the previous dose, rather than after 24 hours. This resulted in residual drug concentration and a shorter period to reach maximal serum concentration. On day 1, $T_{1/2}$ was 2.4 ± 0.4 hr (range: 0.4 to 5.1 hr). After repeated dosing, $T_{1/2}$ was 2.5 ± 0.4 hr (range: 0.7 to 4.2 hr). AUC was 796 ± 159 ng hr/mL after the first dose and 818 ± 170 ng• hr/mL after repeated dosing. Zolpidem was not hemodialyzable. No accumulation of unchanged drug appeared after 14 or 21 days. Ambien (zolpidem tartrate) pharmacokinetics were not significantly different in renally impaired patients. No dosage adjustment is necessary in patients with compromised renal function. As a general precaution, these patients should be closely monitored.

Postulated relationship between elimination rate of hypnotics and their profile of common untoward effects: The type and duration of hypnotic effects and the profile of unwanted effects during administration of hypnotic drugs may be influenced by the biologic half-life of administered drug and any active metabolites formed. When half-lives are long, drug or metabolites may accumulate during periods of nightly administration and be associated with impairment of cognitive and/or motor performance during waking hours; the possibility of interaction with other psychoactive drugs or alcohol will be enhanced. In contrast, if half-lives, including half-lives of active metabolites, are short, drug and metabolites will be cleared before the next dose is ingested, and carryover effects related to excessive sedation or CNS depression should be minimal or absent. Ambien has a short half-life and no active metabolites. During nightly use for an extended period, pharmacodynamic tolerance or adaptation to some effects of hypnotics may develop. If the drug has a short elimination half-life, it is possible that a relative deficiency of the drug or its active metabolites (ie, in relationship to the receptor site) may occur at some point in the interval between each night's use. This sequence of events may account for two clinical findings reported to occur after several weeks of nightly use of other rapidly eliminated hypnotics, namely, increased wakefulness during the last third of the night, and the appearance of increased signs of daytime anxiety. Increased wakefulness during the last third of the night as measured by polysomnography has not been observed in clinical trials with Ambien.

Controlled trials supporting safety and efficacy

Transient insomnia: Normal adults experiencing transient insomnia (n=462) during the first night in a sleep laboratory were evaluated in a double-blind, parallel group, single-night trial comparing two doses of zolpidem (7.5 and 10 mg) and placebo. Both zolpidem doses were superior to placebo on objective (polysomnographic) measures of sleep latency, sleep duration, and number of awakenings.

Normal elderly adults (mean age 66) experiencing transient insomnia (n=35) during the first two nights in a sleep laboratory were evaluated in a double-blind, crossover, 2-night trial comparing four doses of zolpidem (5, 10, 15 and 20 mg) and placebo. All zolpidem doses were superior to placebo on the two primary PSG parameters (sleep latency and efficiency) and all four subjective outcome measures (sleep duration, sleep latency, number of awakenings, and sleep quality).

Chronic insomnia: Zolpidem was evaluated in two controlled studies for the treatment of patients with chronic insomnia (most closely resembling primary insomnia, as defined in the APA Diagnostic and Statistical Manual of Mental Disorders, DSM-IV™). Adult outpatients with chronic insomnia (n=75) were evaluated in a double-blind, parallel group, 5-week trial comparing two doses of zolpidem tartrate (10 and 15 mg) and placebo. On objective (polysomnographic) measures of sleep latency and sleep efficiency, zolpidem 15 mg was superior to placebo for all 5 weeks; zolpidem 10 mg was superior to placebo on sleep latency for the first 4 weeks and on sleep efficiency for weeks 2 and 4. Zolpidem was comparable to placebo on number of awakenings at both doses studied.

Adult outpatients (n=141) with chronic insomnia were also evaluated in a double-blind, parallel group, 4-week trial comparing two doses of zolpidem (10 and 15 mg) and placebo. Zolpidem 10 mg was superior to placebo on a subjective measure of sleep latency for all 4 weeks, and on subjective measures of total sleep time, number of awakenings, and sleep quality for the first treatment week. Zolpidem 15 mg was superior to placebo on a subjective measure of total sleep latency for the first 3 weeks, on a subjective measure of total sleep time for the first week, and on number of awakenings and sleep quality for the first 2 weeks.

Next-day residual effects: Next-day residual effects of Ambien were evaluated in seven studies involving normal volunteers. In three studies in adults (including one study in a phase advance model of transient insomnia) and in one study in elderly subjects, a small but statistically significant decrease in performance was observed in the Digit Symbol Substitution Test (DSST) when compared to placebo. Studies of Ambien in non-elderly patients with insomnia did not detect evidence of next-day residual effects using the DSST, the Multiple Sleep Latency Test (MSLT), and patient ratings of alertness.

Rebound effects: There was no objective (polysomnographic) evidence of rebound insomnia at recommended doses seen in studies evaluating sleep on the nights following discontinuation of Ambien (zolpidem tartrate). There was subjective evidence of impaired sleep in the elderly on the first post-treatment night at doses above the recommended elderly dose of 5 mg.

Memory impairment: Controlled studies in adults utilizing objective measures of memory yielded no consistent evidence of next-day memory impairment following the administration of Ambien. However, in one study involving zolpidem doses of 10 and 20 mg, there was a significant decrease in next-morning recall of information presented to subjects during peak drug effect (90 minutes post-dose), ie, these subjects experienced anterograde amnesia. There was also subjective evidence from adverse event data for anterograde amnesia occurring in association with the administration of Ambien, predominantly at doses above 10 mg.

Effects on sleep stages: In studies that measured the percentage of sleep time spent in each sleep stage, Ambien has generally been shown to preserve sleep stages. Sleep time spent in stages 3 and 4 (deep sleep) was found comparable to placebo with only inconsistent, minor changes in REM (paradoxical) sleep at the recommended dose.

INDICATIONS AND USAGE

Ambien (zolpidem tartrate) is indicated for the short-term treatment of insomnia. Ambien has been shown to decrease sleep latency and increase the duration of sleep for up to 35 days in controlled clinical studies (see *Clinical Pharmacology: Controlled trials supporting safety and efficacy*).

Hypnotics should generally be limited to 7 to 10 days of use, and reevaluation of the patient is recommended if they are to be taken for more than 2 to 3 weeks. Ambien should not be prescribed in quantities exceeding a 1-month supply (see *Warnings*).

CONTRAINDICATIONS

None known.

WARNINGS

Since sleep disturbances may be the presenting manifestation of a physical and/or psychiatric disorder, symptomatic treatment of insomnia should be initiated only after a careful evaluation of the patient. The failure of insomnia to remit after 7 to 10 days of treatment may indicate the presence of a primary psychiatric and/or medical illness which should be evaluated. Worsening of insomnia or the emergence of new thinking or behavior abnormalities may be the consequence of an unrecognized psychiatric or physical disorder. Such findings have emerged during the course of treatment with sedative/hypnotic drugs, including Ambien. Because some of the important adverse effects of Ambien appear to be dose related (see *Precautions* and *Dosage and Administration*), it is important to use the smallest possible effective dose, especially in the elderly.

A variety of abnormal thinking and behavior changes have been reported to occur in association with the use of sedative/hypnotics. Some of these changes may be characterized by decreased inhibition (eg, aggressiveness and extroversion that seemed out of character), similar to effects produced by alcohol and other CNS depressants. Other reported behavioral changes have included bizarre behavior, agitation, hallucinations, and depersonalization. Amnesia and other neuro-psychiatric symptoms may occur unpredictably. In primarily depressed patients, worsening of depression, including suicidal thinking, has been reported in association with the use of sedative/hypnotics.

It can rarely be determined with certainty whether a particular instance of the abnormal behaviors listed above is drug induced, spontaneous in origin, or a result of an underlying psychiatric or physical disorder. Nonetheless, the emergence of any new behavioral sign or symptom of concern requires careful and immediate evaluation.

Following the rapid dose decrease or abrupt discontinuation of sedative/hypnotics, there have been reports of signs and symptoms similar to those associated with withdrawal from other CNS-depressant drugs (see *Drug Abuse and Dependence*).

Ambien, like other sedative/hypnotic drugs, has CNS-depressant effects. Due to the rapid onset of action, Ambien should only be ingested immediately prior to going to bed. Patients should be cautioned against engaging in hazardous occupations requiring complete mental alertness or motor coordination such as operating machinery or driving a motor vehicle after ingesting the drug, including potential impairment of the performance of such activities that may occur the day following ingestion of Ambien. Ambien showed additive effects when combined with alcohol and should not be taken with alcohol. Patients should also be cautioned about possible combined effects with other CNS-depressant drugs. Dosage adjustments may be necessary when Ambien is administered with such agents because of the potentially additive effects.

PRECAUTIONS

General

Use in the elderly and/or debilitated patients: Impaired motor and/or cognitive performance after repeated exposure or unusual sensitivity to sedative/hypnotic drugs is a concern in the treatment of elderly and/or debilitated patients. Therefore, the recommended Ambien dosage is 5 mg in such

Continued on next page

This product information was prepared in September 2003. On these and other products of Sanofi-Synthelabo Inc., detailed information may be obtained on a current basis by direct inquiry to Product Information Services, 90 Park Avenue, New York, NY 10016 (toll free 1-800-446-6267).

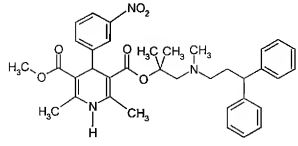
EXHIBIT D

ZANIDIP PRODUCT INFORMATION
(lercanidipine tablets)

DESCRIPTION

Lercanidipine hydrochloride.

Lercanidipine is a dihydropyridine derivative. It is a racemate due to the presence of a chiral carbon atom at position 4 of the 1,4-dihydropyridine ring.



Chemical name: 3,5-pyridinedicarboxylic acid, 1,4- dihydro-2, 6-dimethyl-4-(3-nitrophenyl)-2-[(3,3-diphenylpropyl)methylamino]-1,1-dimethylethyl methyl ester hydrochloride. MW: 648.2 (free base: 611.7).

Lercanidipine hydrochloride (CAS: 132866-11-6) is a microcrystalline, odourless, citrine powder, readily soluble in chloroform and methanol, practically insoluble in water. Octanol:water partition coefficient (LogP): 6.4.

Zanidip tablets also contain the excipients lactose, microcrystalline cellulose, sodium starch glycollate, povidone and magnesium stearate. The tablets are film–coated with the proprietary ingredients Opadry OY-SR-6497 (10 mg-yellow) or Opadry O2-F2-5077 (20 mg-pink).

PHARMACOLOGY

Pharmacodynamic Properties

Lercanidipine is a calcium antagonist of the dihydropyridine group and selectively inhibits the transmembrane influx of calcium into cardiac and vascular smooth muscle, with a greater effect on vascular smooth muscle than on cardiac smooth muscle. The antihypertensive action is due to a direct relaxant effect on vascular smooth muscle which lowers total peripheral resistance and hence blood pressure. Lercanidipine has a prolonged antihypertensive activity because of its high membrane partition coefficient. It is devoid of negative inotropic effects and its vascular selectivity is due to its voltage-dependent calcium antagonist activity. Since the vasodilatation induced by lercanidipine hydrochloride is

gradual in onset, acute hypotension with reflex tachycardia has rarely been observed in hypertensive patients.
As for other asymmetric 1,4-dihydropyridines, the antihypertensive activity of lercanidipine is mainly due to the (S) – enantiomer.
No significant effects on ECG have been seen.

Clinical Trials

Placebo-controlled studies

Lercanidipine has been compared to placebo in four (4) to 16-week studies, involving 671 patients with mild-moderate essential hypertension. All studies used a 3-week placebo run-in period. Endpoints were diastolic and systolic blood pressure 24 hours post dose. Both 10mg and 20mg once daily significantly lowered diastolic and systolic blood pressure compared to placebo, and the reduction in blood pressure was maintained throughout the 24 hour dosing period.
Diastolic blood pressure changes observed after 4-week treatment with 10-20 mg QD lercanidipine ranged between 8 and 13 mmHg, as compared to 3-6 mmHg induced by placebo.
Studies with 24-hour ambulatory blood pressure monitoring have documented that the antihypertensive effect of lercanidipine is maintained throughout the 24 hour dosing period, with limited variations between peak (5-7 hours post dosing) and trough blood pressure changes.

Active-controlled studies

Four clinical trials involving 538 patients with mild-moderate essential hypertension have compared lercanidipine with nifedipine SR, atenolol, hydrochlorothiazide and captopril. Trials included a 2-week washout period followed by a 3-week placebo run-in, and 12-16 weeks of active treatment. Diastolic and systolic blood pressure was measured 24 hours post-dose. Lercanidipine was as effective as the comparator drugs, and at least as well tolerated. 24-hour blood-pressure monitoring was used in a comparative, cross-over trial of lercanidipine versus amlodipine (n=16). The effect of lercanidipine paralleled that of amlodipine throughout the 24 hour period.

Patients with Isolated Systolic Hypertension

The effect of lercanidipine 10-20mg daily on isolated systolic hypertension was studied in a double-blind, randomised, placebo-controlled study in 83 elderly patients (sitting SBP>160mm Hg and sitting DBP<95mm Hg). The study consisted of 1 week wash-out, 3 weeks placebo run-in, and 8 weeks of active treatment. Systolic and diastolic blood pressure was measured 24 hours post dose. Lercanidipine 10 to 20 mg was efficacious in lowering systolic blood pressure from the initial values of 172.6+ 5.6 mmHg to 140.2+ 8.7mmHg (mean±SD, per-protocol population in all patients completing the whole 8 weeks of double-blind treatment), as compared to the changes in the placebo group (from 172.4±6.3 to 162.8±9.7 mmHg). Therefore, at study endpoint, patients treated with lercanidipine experienced a significantly greater decrease (-22.6mm Hg, $p<0.001$) in sitting systolic blood pressure in comparison to placebo. The diastolic blood pressure was within normal range.

Long-term studies
In long term studies, 399 patients were followed for 12 months, with dose titration allowed every 4 weeks, to 30mg daily. Development of tolerance was not seen. The antihypertensive effect was maintained, and the heart rate was not significantly affected. A further fall in blood pressure was seen after the first and second month, with blood pressure stabilising in the third month. The majority of patients remained on 10mg once daily.

Pharmacokinetics
Absorption
Lercanidipine is completely absorbed after oral administration. Peak plasma levels of 3.30ng/mL ± 2.09 s.d and 7.66 ng/mL ± 5.90 s.d occur 1.5-3 hours after dosing with 10mg and 20mg, respectively. The absolute bioavailability of lercanidipine is about 10%, because of high first pass metabolism. The bioavailability increases 4-fold when lercanidipine is ingested up to 2 hours after a high fat meal, and about 2-fold when taken immediately after a carbohydrate-rich meal. Consequently, lercanidipine should be taken at least 15 minutes before a meal.
With oral administration, lercanidipine exhibits non-linear kinetics. After 10, 20 or 40mg, peak plasma concentrations observed were in the ratio 1:3:8 and areas under plasma concentration-time curves in the ratio 1:4:18, showing a progressive saturation of first pass metabolism. Accordingly, bioavailability increases as dosage increases.
The two enantiomers of lercanidipine have a similar time to peak plasma concentration. The peak plasma concentration and AUC are, on average, 1.2-fold higher for the (S) enantiomer. No *in vivo* interconversion of enantiomers is observed.
Distribution
Distribution of lercanidipine from plasma to tissues and organs is rapid and extensive. Serum protein binding exceeds 98%. The free fraction of lercanidipine may be increased in patients with renal or hepatic impairment as plasma protein levels are decreased in these disease states.
Metabolism
As for other dihydropyridine derivatives, lercanidipine is extensively metabolised by CYP3A4. It is predominantly converted to inactive metabolites; no parent drug is found in the urine or faeces. About 50% of the dose is excreted in the urine.
Elimination
The mean terminal elimination half-life of S- and R-lercanidipine enantiomers is 5.8±2.5 and 7.7±3.8 hours, respectively. No accumulation was seen upon repeated administration. The therapeutic activity of lercanidipine lasts for 24 hours, due to its high binding to lipid membranes.
Elderly patients
In elderly patients, the pharmacokinetics of lercanidipine is similar to that observed in the general population.

Hepatic Impairment
A study in patients with mild hepatic impairment (Child-Pugh class A) showed that the pharmacokinetic behaviour of the drug is similar to that observed in the general population. No studies have been undertaken in patients with moderate or severe hepatic impairment.

Renal impairment
In patients with severe renal dysfunction (creatinine clearance < 12mL/min) or dialysis-dependent patients, plasma levels were increased by about 70%. As a consequence, the drug should be contraindicated in severe renal impairment.

INDICATIONS
Zanidip is indicated for the treatment of hypertension.

CONTRAINDICATIONS
- Hypersensitivity to any dihydropyridine or any ingredient of Zanidip;
- Severe hepatic impairment;
- Severe renal impairment (creatinine clearance < 12 mL/min).
- Concomitant treatment of Zanidip with cyclosporin should be avoided

PRECAUTIONS
Ischaemic heart disease
It has been suggested that some short-acting dihydropyridines may be associated with increased cardiovascular risk in patients with ischaemic heart disease. Although lercanidipine is long-acting, caution should be required in such patients.
Outflow obstruction (aortic stenosis)
Lercanidipine should be administered with caution in patients with left ventricular outflow obstruction (aortic stenosis).
Congestive heart failure
In general calcium channel blockers should be used with caution in patients with heart failure. Although animal data and acute haemodynamic evaluation in patients with preserved left ventricular function have not demonstrated that lercanidipine exerts a direct negative inotropic effect, safety in patients with congestive heart failure has not been established. Therefore, as for other calcium channel blockers, lercanidipine should be used with caution in such patients, especially if untreated.
Unstable angina pectoris or within one month of a myocardial infarction
Rarely patients have developed documented increased frequency, duration and/or severity of angina on starting calcium channel blocker therapy or at the time of dosage increase (particularly those with severe obstructive coronary artery disease). The mechanism of this effect has not been elucidated, however the possibility of an exacerbation of angina and/or cardiac ischaemia exists. It is therefore suggested that the use of

calcium channel blockers is not advisable in patients with unstable angina pectoris or recent myocardial infarction.

Carcinogenesis, mutagenesis, impairment of fertility

No evidence for genotoxic activity was observed with lercanidipine in *in vitro* assays of gene mutation (reverse mutation in S. Typhimurium, forward mutation in Chinese Hamster V79 fibroblasts), gene conversion (in saccharomyces cerevisiae D4) or chromosomal damage (CHO cytogenetic assay). Negative findings were also obtained with lercanidipine in an *in vivo* assay of chromosomal damage (mouse micronucleus test).

Carcinogenicity studies of lercanidipine (administered *via* the diet) have been performed in rats and mice (18 months), using doses up to 60 mg/kg/day for mice and 5 mg/kg/day for rats. Plasma concentrations (AUC) of lercanidipine at the highest doses used in these studies were about 2-4 times the highest AUC expected in humans during treatment with lercanidipine. Lercanidipine showed no evidence of carcinogenic activity in these studies.

Administration of lercanidipine at oral doses up to 12 mg /kg /day (associated with plasma lercanidipine concentration (AUC) about 20-40 times higher than the expected human AUC) had no effect in male or female fertility in rat.

Use in pregnancy: Category C

There is no clinical experience with lercanidipine in pregnancy, but other dihydropyridine compounds have been found to cause irreversible malformations in animals. Therefore, lercanidipine should not be administered during pregnancy or to women with child-bearing potential unless effective contraception is used.

In animal studies, pregnant rats given lercanidipine orally at doses $\geq$ 2.5 mg/kg/day, beginning prior to mating, or 12 mg/kg/day, beginning from early gestation, showed signs of distocia and had a increased incidence of still births and a lower neonatal survival index. The no-effect dose for effects on parturition and neonatal survival was 0.5 mg/kg/day (associated with lercanidipine concentration (AUC) about 50% of the expected human AUC) when dosing started before pregnancy or 2.5 mg/kg/day (about 3 times the human AUC) when dosing started during early gestation. Administration with lercanidipine at doses of 2.5 mg/kg/day during gestation also caused a higher incidence of fetal visceral abnormalities (mono/bilateral renal pelvic and/or ureteric dilatation) and skeletal abnormalities (mainly delayed ossification) at all dose levels. A no-effect dose was not established. The effects of lercanidipine during pregnancy have not been investigated adequately in a non-rodent species.

Use in lactation

There is no clinical experience with lercanidipine in lactation. Distribution into milk may be expected, due to the high lipophilicity of lercanidipine. Therefore, lercanidipine should not be administered to lactating women.

Use in the elderly

Although the pharmacokinetic data and clinical experience suggest that no adjustment of the daily dose is required, special care should be exercised when initiating treatment in the elderly.

Use in children

Due to lack of clinical experience, lercanidipine is not recommended for use in patients under the age of 18.

Use in hepatic impairment

The pharmacokinetics of lercanidipine in patients with mild hepatic impairment are similar to those observed in the general population. However, there are no studies in patients with moderate hepatic impairment and dosage recommendations have not been established. Lercanidipine should therefore be used with caution in this patient group and careful monitoring undertaken during treatment, since the bioavailability and hypotensive effect may be increased. The use of Lercanidipine in patients with moderate hepatic impairment should only be undertaken if the benefits are considered to outweigh the risks. Lercanidipine is contraindicated, in patients with severe hepatic disease.

Use in renal impairment

Although the pharmacokinetics of lercanidipine in patients with mild to moderate renal impairment are similar to those observed in the general population, special care should be exercised when commencing the treatment in such patients. The usual recommended dose of 10mg daily may be tolerated; however, an increase to 20mg daily should be approached with caution.

Interaction with other drugs

Lercanidipine has been safely administered with diuretics and ACE inhibitors. It may also be administered safely with beta-blockers which are eliminated unchanged (such as atenolol).

Inhibitors or inducers of Cytochrome CYP3A4

Since the main metabolic pathway of lercanidipine involves the enzyme CYP3A4, drugs that inhibit or induce this enzyme have the potential to alter the plasma concentration of the compound.

Therefore, inhibitors of CYP3A4 (such as ketoconazole, itraconazole, erythromycin, ritonavir and fluoxetine) may increase the plasma concentration of lercanidipine, and such combinations should be used with caution.

When co-administered with CYP3A4 inducers, such as anticonvulsants (eg. phenytoin, carbamazepine) and rifampicin, the antihypertensive effect of lercanidipine may be reduced and, therefore, blood pressure should be monitored when the co-administration is foreseen.

CYP3A4 and CYP2D6 substrates

The potential for *in vivo* inhibition of CYP3A4 by lercanidipine is negligible, as confirmed by an interaction study with midazolam in healthy volunteers. After repeated co-administration with lercanidipine, midazolam (a probe for CYP3A4 activity) was found to be essentially bioequivalent to the drug administered alone. However, unless specific data are available, caution should also be exercised when lercanidipine is co-prescribed with other substrates of CYP3A4 which have a narrow therapeutic index, such as cyclosporin, and class III antiarrhythmic drugs (e.g. amiodarone and quinidine).

Co-administration of lercanidipine with cyclosporin resulted in a 3 fold increase in the plasma levels of lercanidipine and a 21% increase in the bioavailability of cyclosporin. However, when cyclosporin was administered 3 hours after lercanidipine, no increase in plasma levels was observed for lercanidipine, while the bioavailability of cyclosporin

increased by 27%. Therefore, cyclosporin and lercanidipine should not be administered together.
Moreover, interaction studies in humans have shown that lercanidipine did not modify the plasma levels of metoprolol, (a typical substrate of CYP2D6). Therefore, at therapeutic doses it is unlikely that lercanidipine will inhibit the biotransformation of drugs metabolized by CYP2D6.
These findings confirm that the inhibition of cytochrome P450 isoenzymes observed *in vitro* with lercanidipine is devoid of any clinical significance. *In vitro* experiments with human liver microsomes demonstrated that lercanidipine inhibits CYP3A4 and CYP2D6 (IC_{50} of 2.6 µm and 0.8 µm, respectively). The IC_{50} concentrations for CYP3A4 and CYP2D6 are 160 and 40 fold higher, respectively, than those reached at peak in the plasma after a 20mg dose.

Beta-blockers

When lercanidipine was administered with metoprolol, a beta-blocker eliminated mainly by the liver, the bioavailability of metoprolol was not changed, while that of lercanidipine was reduced by 50%. Therefore, when co-administered with metoprolol, it may be necessary to increase the dose of lercanidipine. It is anticipated that a similar effect may occur with propranolol.

Cardiac glycosides

Co-administration of lercanidipine in patients chronically treated with beta-methyldigoxin (a pro-drug of digoxin) showed no evidence of a pharmacokinetic interaction. However, patients on concomitant digoxin treatment should be closely monitored.

Cimetidine

Concomitant administration of cimetidine 400mg BD does not cause significant changes in the plasma levels of lercanidipine: AUC and Cmax were increased by a mean of 11%. However, at higher doses caution is required since the bioavailability and the hypotensive effect of lercanidipine may be increased.

Simvastatin

Co-administration of a 20 mg dose of lercanidipine with 40 mg simvastatin resulted in no increase in the bioavailability of lercanidipine, however a 56% increase was observed for simvastatin and a 28% increase for its active metabolite β-hydroxyacid. It is unlikely that these changes are clinically relevant. However, it is recommended that when required lercanidipine be administered in the morning and simvastatin in the evening.

Food

See previous section on pharmacokinetics.
The metabolism of dihydropyridines can be inhibited by grapefruit juice, leading to increased plasma concentration and hypotensive effect.
Alcohol should be avoided while taking lercanidipine since it may potentiate the effect of vasodilating antihypertensive drugs.

ADVERSE REACTIONS

Treatment with lercanidipine is generally well tolerated. In nine placebo-controlled clinical trials with a treatment duration lasting at least 4 weeks, 582 patients were initially treated with lercanidipine, and 292 patients received placebo. Most of the events reported in the studies were related to the vasodilatory effects of lercanidipine, and were classified mild-moderate in severity.

Table 1 lists, according to organ system, adverse events that were reported in placebo controlled trials in hypertensive patients with lercanidipine tablets at an incidence greater than or equal to 1% in at least one of the active treatment groups.

Table 1

Adverse Event	Lercanidipine 10mg once daily (%)	Lercanidipine 20mg once daily (titrated) (%)	Placebo (%)
CARDIOVASCULAR			
Flushing	**2.6**	**2.2**	**1.6**
Palpitations/Tachycardia	**1.5**	**1.1**	**0.3**
BODY AS A WHOLE			
Peripheral oedema	**1.0**	**1.1**	**0.9**
CENTRAL & PERIPHERAL NERVOUS SYSTEM			
Dizziness	**1.0**	**0.0**	**0.6**
Headache	**4.4**	**4.3**	**2.5**
LIVER DISORDERS			
GGT increased	**0.0**	**1.1**	**0.3**

More extensively, over 15500 patients were treated with lercanidipine in clinical trials (including PMS studies) with doses from 2.5 mg QD up to 40 mg QD, and with treatment duration ranging from single dose up to more than 1 year. Adverse experiences which were not clearly drug related and which occurred in <1% but ≥0.1% of patients are summarized according to organ system.

Cardiovascular: palpitations/tachycardia.
Central and Peripheral nervous system: dizziness, vertigo.
Gastrointestinal: nausea, dyspepsia, abdominal pain, diarrhoea.
Psychiatric: somnolence.
General: flushing, asthenia (including fatigue and muscle weakness).

The following events have been rarely reported:
Cardiovascular: hypotension, orthostatic hypotension, periorbital oedema, anginal pain, myocardial infarction, cardiac failure.
Respiratory: dyspnoea.
Central and Peripheral nervous system: migraine, paraesthesia, cramps legs.

Special senses: taste alteration.
Gastrointestinal: vomiting, GI disorder NOS.
Liver and biliary system: GGT increased.
Genitourinary: polyuria, urinary frequency, impotence.
Musculoskeletal: myalgia.
Skin and appendages: rash, pruritus, allergic dermatitis, hives, sweating increased.
Psychiatric: anxiety, insomnia.
Metabolic: Hypercholesterolaemia.
General: chest pain, malaise.
Serious adverse events have been reported in clinical trials in less than 0.002% of the patients. The remaining adverse events have been reported as mild to moderate in intensity.

Laboratory tests
There were reports of isolated and reversible increases in serum levels of hepatic transaminases; no other clinically significant pattern of laboratory test abnormalities related to lercanidipine has been observed. Lercanidipine does not effect blood sugar or lipid levels.

DOSAGE AND ADMINISTRATION
The recommended dose is 10mg once daily, at least 15 minutes before a meal. The dose may be increased to 20mg once daily depending on the individual response. Dose titration should be gradual, as it may take about 2 weeks for the maximal antihypertensive effect to be apparent. Titration may proceed more rapidly, however, if clinically warranted, provided the patient is assessed frequently. Since it is unlikely that increasing the dose beyond 20mg will further improve the efficacy, and may be associated with side effects, doses above 20 mg are not recommended. Some individuals not adequately controlled on a single antihypertensive agent may benefit from the addition of lercanidipine at the same doses used in monotherapy to the existing regimen with a beta-blocker, a diuretic or an ACE-inhibitor.

Use in elderly, children, hepatic and renal impairment: see precautions.

OVERDOSAGE
There is no experience with lercanidipine overdosage. As with other dihydropyridines, overdosage might be expected to cause excessive peripheral vasodilation with marked hypotension and reflex tachycardia. In case of severe hypotension, bradycardia and unconsciousness, cardiovascular and respiratory monitoring will be required, and supportive treatment may be necessary. Since lercanidipine is highly lipophilic, dialysis is unlikely to be effective.

PRESENTATION

ZANIDIP is available as 10 mg or 20 mg tablets.
10 mg: Yellow, round, scored, film-coated tablets, containing lercanidipine 9.4 mg (present as 10mg of lercanidipine hydrochloride).
20 mg: Pink, circular, biconvex, film-coated tablets, containing lercanidipine 18.8 mg (present as lercanidipine hydrochloride 20 mg).
Packs of 7 or 30 tablets.

STORAGE

Store below 30 degrees Celsius. Protect from moisture and light.

NAME AND ADDRESS OF THE SPONSOR

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DATE OF TGA APPROVAL

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